THE RELATION BETWEEN RHEUMATOID ARTHRITIS, SARS-COV-2, MEDICATION AND VACCINATION.

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Summary

Rheumatoid arthritis (RA) is an autoimmune disease, attacking the joints throughout the body via autoantibodies. Various therapies are available for patients, including IL-6 and TNF inhibitors, anti-B cell therapy via anti-CD20 antibodies and inhibitors of the JAK/STAT pathway. As these drugs do not only inhibit the autoreactive antibodies, but also the other non-self-antibodies and may have an effect on T cells, the therapies also have an effect on the regular immune system of the patient. With the world in a state of the pandemic of SARS-CoV-2, infections are more prone than before. This study focuses on the efficacy and safety of the available vaccines, as well as medication used to battle the COVID-19 disease. Serological values in RA patients post-vaccination show a slower process in obtaining the same amount of specific IgGs, compared to healthy controls. Especially patients taking broad-spectrum medication encounter worse results post-vaccination than patients with a specific drug. Despite the lowered number of B cells present in many of the therapy forms, the T cell immune response is often comparable to that of healthy controls. Interestingly, baricitinib, RA medication, is also used in hospitals in a way to battle COVID-19. The RA medications help to reduce the inflammation caused by the diseases. A third dose of vaccination appears to have some influence on humoral immunity, but it is advised to extend the time between these vaccinations when B cell depleting therapy is used.
Despite the fact that the humoral response is significantly dampened in RA patients, the T cell immune response still occurs, providing some immunity to the patients. It is therefore safe and effective for RA patients to receive COVID-19 vaccination.

List of Abbreviations

- ACE2 – Transmembrane angiotensin-converting enzyme 2
- ACPA – Anticitrullinated protein antibodies
- ACR/EULAR – American College of Rheumatology and the European League Against Rheumatism
- CXCL10 – C-X-C motif chemokine ligand 10
- DMARD – Disease-modifying antirheumatic drug
- FLS – Fibroblast-like synoviocytes
- IFN – Interferon
- JAK – Janus kinase
- JAKinib – Janus kinase inhibitor
- MTX – Methotrexate
- RA – Rheumatoid Arthritis
- RF – Rheumatoid factor
- RTX – Rituximab
- SARS-CoV-2 – Severe acute respiratory syndrome coronavirus-2
- TCR – T cell receptor
- TNF – Tumor necrosis factor

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1. Rheumatoid Arthritis.

Rheumatoid Arthritis (RA) is an autoimmune disease, targeting mainly diarthrodial joints, and, as of 2010, affects 0.5-1.0% of adults (Scott, Wolfe & Huizinga, 2010). The joints are inflamed, which can result in an enlarged and warm feeling of the joints. The persistent inflammation is cause for damage to articular cartilage and underlying bone (Scott et al., 2010). While the origin and stimulation factors to develop RA are still unsure, the biological process after onset of the disease becomes more and more clear. There are various inflammatory cascades involved in RA. One of the inflammatory cascades involves overexpression and overproduction of tumor necrosis factor (TNF). TNF-α is the culmination of this pro-inflammatory cascade. At a chronic inflammatory site, there are also upregulations of various anti-inflammatory mediators, such as IL-10 and IL-1ra (Feldman, Brennan & Maini, 1996). Overexpression of TNFα leads to the overproduction of various cytokines like interleukin (IL-) 6 and IL-1 (Scott et al., 2010). The synovial tissue contains various non-immune cell types, such as fibroblast-like synoviocytes (FLS), that contribute to joint destruction in RA by the production of bone- and cartilage degrading enzymes (Schellekens et al., 2010; Yoshitomi, 2019). The FLSs secrete chemo-attractants after activation via the cytokines, which attracts monocytes and macrophages. The macrophages excrete IL-1 and TNF-α, which in turn recruits more macrophages, resulting in the local expansion of macrophages (Yoshitomi, 2019). Therapy aimed at TNF and/or IL-6 inhibition works relatively well as treatment. Weinblatt et al stated in 2013 that treatment that targets T cells, is also effective (Weinblatt et al., 2013). As autoantibodies are involved in RA, the CD4+ helper T cells are mainly active in the function of B cell help (Yoshitomi, 2019). Preventing B cells to fully mature, is also an effective way to obtain clinically good results for RA. Administration of B-cell-depleting anti-CD20 antibody is an effective way to prevent maturation (Doorenspleet et al., 2014; Edwards et al., 2004) Figure 1 shows an adapted version of figure 6 from the 2021 study performed by Akram et al., showing a schematic overview of the immune response in RA.

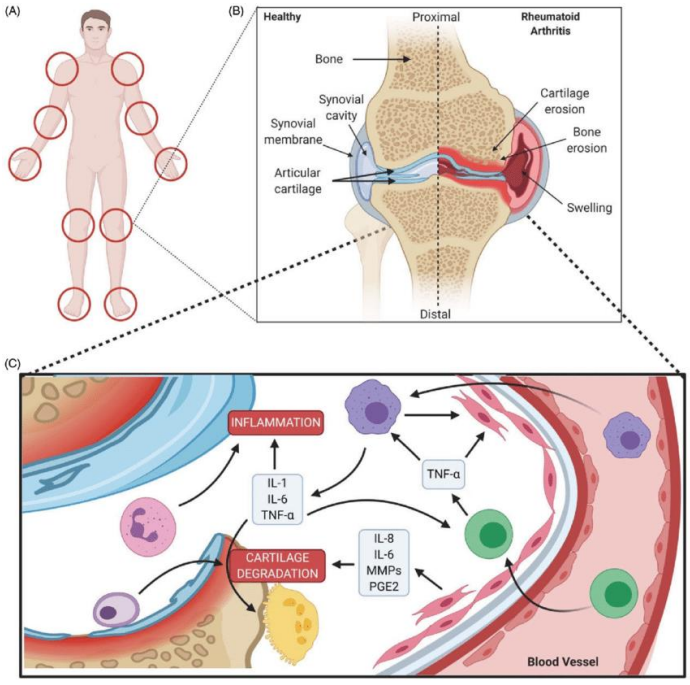

Figure 1: Pathophysiology of rheumatoid arthritis. Adapted from Akram et al., 2021. (A) Possible areas for RA. (B) A healthy synovial joint (left) and the impact of RA (right). (C) Mechanism of RA within the joint capsule.

As RA is an autoimmune disease, autoantibodies are involved in the diagnosis as biomarkers (Atzeni et al., 2017; Scott et al., 2010). Rheumatoid factor (RF) positive levels may increase the risk of developing RA, however, RF positivity on its own is not sufficient (Castro & Gourley, 2010), as people without RA can show similar titer levels (Wolfe, Cathey & Roberts, 1991). Anticitrullinated protein antibody (ACPA) is an RA-specific autoantibody. ACPA positive levels can be noted years prior to the clinical onset of RA. Higher levels of ACPA may also indicate an increased probability of bone erosions, seen on radiographic images (van der Linden et al., 2009; Szodorav et al., 2010). The symptoms of RA can be similar to that of other diseases, therefore, before diagnosing, the patient has to be tested for various of these other ailments, such as Hepatitis B, tuberculosis and, when possible, undergo radiotherapies, such as X-Ray or ultrasound. In 2010, a list of updated classification criteria was created for diagnosis of RA, by both the American College of Rheumatology and the European League Against Rheumatism (ACR/EULAR). The criteria include the number of joints involved in the inflammation, serology levels of various biomarkers indicating RA, acute phase reactants, and the symptoms' duration. The score of these criteria has to be a score of 6 or greater (Aletaha et al., 2010). Table 1 represents the scoring mechanism ACR/EULAR created, copied from the respective article, table 3.

Table 1: ACR/EULAR classification criteria for RA. Adopted from Aletaha et al (2010), table 3.

	Score
Target population (Who should be tested?): Patients who	
1) have at least 1 joint with definite clinical synovitis (swelling)	
2) with the synovitis not better explained by another disease	
Classification criteria for RA (score-based algorithm: add score of categories A-D; a score of ≥6/10 is needed for classification of a patient as having definite RA)	
A. Joint involvements	
1 large joint	0
2 – 10 large joints	1
1 – 3 small joints (with or without involvement of large joints)	2
4 – 10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	
Normal CRP and normal ESR 0	0
Abnormal CRP or normal ESR 1	1
D. Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

There are various therapies that can be used in battling RA. These drugs include non-steroidal anti-inflammatory drugs, disease-modifying anti-rheumatic drugs (DMARDs) of synthetic origin, such as methotrexate (MTX) or Janus kinase (JAK)-inhibitors, or biological origins, such as TNF and IL-6 inhibitors and B-cell-depleting anti-CD20 (Bumerster & Pope, 2017; Chatzidionysiou et al., 2017). Patients typically start with MTX therapy, post-diagnosis, as this is one of the conventional DMARDs (cDMARDs). MTX can be given solely, as well as in combination with other drugs, as biological DMARDs (bDMARDs). This results in the understanding that MTX should be given as the first line of therapy, where possible. However, many patients will encounter side effects. (Pincus et al., 2003; Alfaro-Lara et al., 2019). These side effects include but are not limited to, hepatic dysregulations, hematologic disorders, infections, etc. MTX causes a reduction of antigen-dependent T-cell proliferation and has anti-inflammatory effects (Wang W., Zhou & Liu,

2018). Patients undergoing MTX therapy are more susceptible to infections, as well as more severe diseases stemming from these infections (McLean-Tooke et al., 2009).
Another RA drug is baricitinib, part of the targeted synthetic DMARDs (tsDMARDs), and is a JAK inhibitor (JAKinib). Various immune-mediated diseases are associated with JAK/STAT molecules (Wang F. et al., 2020). The accompanying JAK/STAT pathway gets activated by binding various cytokines, including IL-6 and IFNs. Another JAKinib widely used in RA patients is tofacitinib (Fragoulis, McInnes & Siebert, 2019). The JAK inhibitors prevent further gene transcription, stopping the system far before proteins are translated (Fragoulis et al., 2019; Urits et al., 2020).
It was shown that treatment with baricitinib and tofacitinib raises an increased risk of Herpes Zoster virus infections (Sanchez et al., 2018; Fragoulis et al., 2019). By inhibiting IL-6 and its soluble receptor IL-6R, the start of the JAK/STAT pathway can also be inhibited. One of the drugs based on IL-6 inhibition is tocilizumab. The inhibition, therefore, prevents the overactivation of TB cells (Choy, 2004; Tornero Molina et al., 2020). Rituximab (RTX) is an anti-CD20 monoclonal antibody, allowing the depletion of B lymphocytes. It is often given to RA patients that do not show effectivity to csDMARDs (Tavakolpour et al., 2019). This biological was suggested to reduce the mortality rate, compared to DMARDs (Listing et al., 2015).
Studies have shown that the variety in CD4 T cells of RA patients is not as varied as in normal controls. This contraction of T cell receptors (TCR) is seen in mature, as well as naive T cells (Koetz et al., 2000; Martens et al., 1997; Schmidt, Goronzy & Weyand, 1996; Wagner et al., 1998). The study by Koetz et al investigates the possible defect in generating new T cells. The study found that RA patients have a compromised reaction to novel antigens, as well as dysfunction in the reconstitution of the T cell compartment.
As RA is an autoimmune disease, with an inflammatory immune response aimed at the joints of the person's body, it is important to know the effects of additional stimulation of the immune system, for example during an infection or vaccination process. Various studies have shown that HZ infection is more prevalent in RA patients than in the general population, who undergo DMARD, biologics, and/or glucocorticoids (Koh et al., 2018; Harigai, 2019; McDonald et al., 2009; Strangfeld et al., 2009). The study performed by Koh et al. (Koh et al., 2018), showed an increase in specific IgG levels 12 weeks post HZ vaccination in RA patients. While some of the participants experiences a flare of RA, this could not be directly related to vaccination, as the time of flare surpassed the incubation period (Koh et al., 2018).

Due to the fast, global spread of SARS-CoV-2, it is important to know the effects of the virus and possible vaccination for this virus in patients suffering from autoimmune disease(s). In this particular case, the relationship between safety and effectiveness of the viral infection and vaccination is investigated in patients with rheumatoid arthritis.

2. SARS-CoV-2.

Severe acute respiratory syndrome coronavirus-2 (SARS-Cov-2) causes the contagious coronavirus disease COVID-19. SARS-CoV-2 is a respiratory, RNA virus, leading to the disease COVID-19 (Umakanthan et al., 2019). Transmission of the virus occurs via aerosols and infectious respiratory droplets, from the various mucous membranes (Salian et al., 2021). It is known that SARS-CoV-2 uses transmembrane angiotensin-converting enzyme 2 (ACE2) receptors to enter the cell (Rohilla, 2021). This receptor also plays a role in the viral entry of SARS-Cov (Li, Moore & Vasilieva, 2003). The ACE2 receptor can be found in various mammalian tissues, such as the lungs and heart (Mohamadian et al., 2021). It was found that infection mainly occurs in the oral mucosa and the upper and lower respiratory tracts (Salian et al., 2021). After infection, an increase in the release of various pro-inflammatory cytokines and other inflammatory factors as TNF-α and vascular endothelial growth factors are associated with the progression of the disease and the cause of a cytokine storm (Rohilla, 2021). It is also known that acute respiratory distress syndrome occurs when the infection reaches its height in some patients (Mao, Jin & Wang, 2020). While most people will associate coronaviruses with common colds, in elderly people, immune-deficient patients and young children, the disease progression can be worse and more lethal than in other groups (Yesudhas, Srivastava & Gromiha, 2021).

Patients with critical COVID-19 conditions show a decreased level in T and B lymphocytes. These cells, however, play an important role in both the cellular and humoral immune responses.

It is known that STAT3 is contributing to the cytokine storm upon infection by SARS-CoV-2. Therefore, the CD8 T lymphocytes that are stimulated by STAT3 provide one of the main immune responses against COVID-19, which is part of the cause of hyper inflammation. By preventing the activation of STAT3, a reduction of IL-6 can be noted, allowing a knockdown of the hyper inflammation caused by COVID-19 (Satarker et al., 2021). However, immunocompromised people could be susceptible to superinfection by the virus, as inhibiting the JAK/STAT pathway would reduce the inflammation, but not the actual viral clearance (Rojas & Sarmiento, 2020).

There are several drugs that are candidates to combat COVID-19. These include the protease inhibitor furin convertase inhibitor (Rohilla, 2010; Walls et al., 2020) and serine protease inhibitors camostat mesylate and nafamostat mesylate (Rohilla, 2010; Hoffmann et al, 2020). These (serine) protease inhibitors inhibit the non-endosomal viral entry in various mechanisms. The antimalarial drug chloroquine prevents viral entry and arrests disease progression (Rohilla, 2010; Savarino, 2003, 2006). The JAK inhibitor baricitinib is not only a RA drug but was found to also be a candidate for the treatment of COVID-19. It inhibits receptor-mediated endocytosis and suppresses disease progression (Rohilla, 2010; Richardson et al., 2020). In August 2020, a pilot study was published, testing whether baricitinib therapy could be safely and effectively used in treatment for COVID-19, by Cantini et al. Control patients were treated with the standard therapy of lopinavir/ritonavir tablets 250 mg/bid and hydroxychloroquine 400 mg/day/orally, while the test group was also supplemented baricitinib tablets 4 mg/day on top of the standard lopinavir/ritonavir therapy. The study took place over 2 weeks. The study shows that various infection factors and fever significantly improved in the baricitinib-treated group and none of the patients required intensive care support, compared to a third of the control group (Cantini et al., 2020). Other well-studied drugs are the antimalarial drugs chloroquine and hydroxychloroquine. These drugs target the endocytosis pathway and therefore are useful in treating the disease (Yesudhas et al., 2021).

To combat COVID-19 disease, a global race for vaccines was started. Various vaccines have been produced and distributed. In the Netherlands, 4 different manufacturers distributed their respective vaccines, that were provided for their citizens, to varying degrees. The respective vaccines are shown in table 2, representing the reported efficacy and the number of doses required for sufficient immunity, adapted from Chaudhary et al., 2021. Currently, in January 2022, vaccines provided by the Dutch Communal Health Service (GGD, Gemeenschappelijke

Gezondheidsdienst) are mainly from Pfizer and Moderna, due to the side effects in the vaccines from AstraZeneca and Janssen (GGD, 2022). The mRNA vaccines consist of functional mRNA, that encodes for the viral antigen, in particular the Spike proteins. Due to the fact, that the mRNA is functional, the host cells will translate the mRNA, produce the encoded antigen, which in turn yield an immune response. Because of its nature, the nucleic code is not able to integrate into the host's genome (Chaudhary et al., 2021; Kutzler & Weiner, 2008). The viral vector vaccines by Janssen and AstraZeneca show a strong potential to induce cell-mediated immunity (Chaudbury et al., 2021; Sasso et al., 2009; Sasso et al., 2020).

Table 2: COVID-19 vaccines administered in The Netherlands. Adapted from Chaudhary et al. (2021), table 1.

Vaccine manufacturer	Current Dose/Gap and Route of Administration	Vaccine type	Reported efficacy phase 3 (%)
Pfizer / BioNTech (BNT162b2)	Two doses, 21 days apart, intramuscular injection	mRNA	~90
Moderna (mRNA-1273)	Two doses, 28 days apart, intramuscular injection	mRNA	~94.1
AstraZeneca (AZD1222)	Two doses, between 4 and 12 weeks apart, intramuscular injection	Adenovirus vector-based recombinant vaccine	79
Janssen / Johnson (JNJ-78436735; Ad26.COV2.S)	Single dose vaccine, intramuscular injection	Adenovirus vector-based recombinant vaccine	85

Both vaccine types cause dendritic cells to present the S protein, resulting in the release of various cytokines and chemokines. B cells recognize the presented S protein, starting the respective immune response. T cells will bind to MHC class II to then perform their immune response. A visualization is given in figure 2, adapted from Teijaro and Farber (2021).

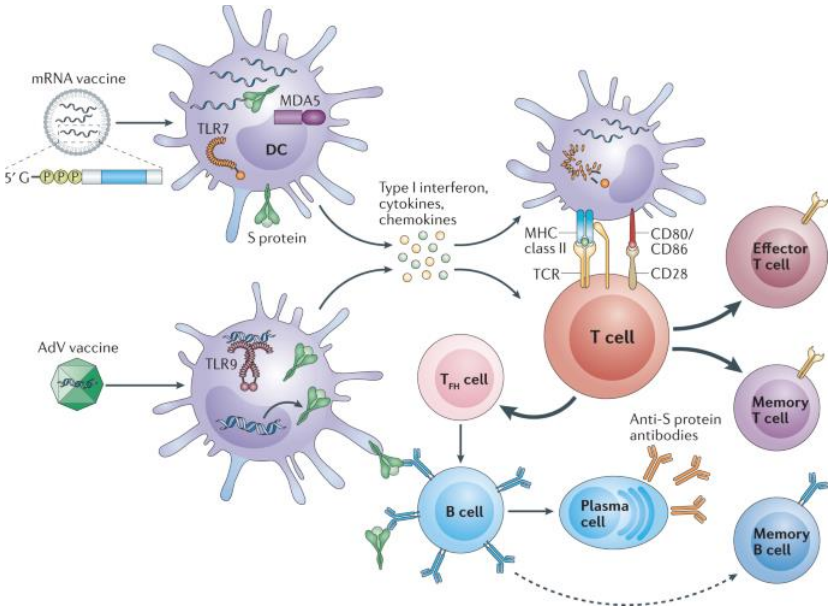

Figure 2: Immune response to mRNA or adenovirus vaccines. Adapted from Teijaro and Farber (2021), figure 1.

3. Rheumatoid Arthritis and COVID-19.

RA patients have a higher risk of getting infected with other diseases and viruses than the general population (Favalli et al., 2020a; Doran et al., 2002). One can also see that the microorganisms may affect the disease progression in an RA patient. Various studies have shown that there is a link between respiratory viral infections and the development of RA and some infections can cause disease flares (Galloway et al., 2011; Listing, Gerhold & Zink, 2013; Joo et al., 2019). Infection with SARS-CoV-2 can trigger inflammatory mediators that are also known in RA pathology, that include C-X-C motif chemokine ligand 10 (CXCL10), IL-17 and TNF-α (Dewanjee et al., 2021).

Treatments suited for COVID-19 were searched for by considering similar viruses as SARS-Cov and MERS-CoV, such as lopinavir and ritonavir (Favalli et al., 2020a; Favalli et al., 2020b). Besides the traditional anti-viral products, various drugs used in RA treatment were proposed as successful therapy, including IL-6 and TNF inhibitors and baricitinib (Favalli et al., 2020a). Baricitinib can inhibit the viral protein targets at approved dosage levels for RA and dampens the host inflammatory response (Sanchez et al., 2018). However, the JAK/STAT blockade generated does result in an impairment of interferon (IFN-α) mediated anti-viral response (Favalli et al., 2020a). A study by Álvaro Gracia (2021) looked into patients with various rheumatoid diseases. They found that patients undergoing B cell-depleting therapy with anti-CD20 showed an increased risk of hospitalization, whereas TNF-inhibitor therapy showed a reduction of the risk. Interestingly, the Álvaro Gracia study did not find a decreased risk of hospitalization after JAK inhibitor therapy, contrary to other reports (Goletti & Cantini, 2021; Seif et al., 2020).

4. Humoral and Cellular Immunity post Vaccination in RA patients.

While in the Netherlands the available vaccinations are/were Pfizer, Moderna, AstraZeneca and Janssen, this varies across the world. Various (severe) side effects were noted to people vaccinated with AstraZeneca and Janssen, resulting in a less prominent amount of vaccinees with these vaccines. Figure 3 shows a graph of the provided vaccines in the Netherlands in the first nine months of 2021, by the Dutch RIVM. Worldwide, most countries use the Pfizer vaccine, followed by AstraZeneca and Moderna (WHO, 2021). It is therefore not surprising that most studies investigating the immune responses in RA patients post-vaccination look into the Pfizer, Moderna and AstraZeneca vaccines.

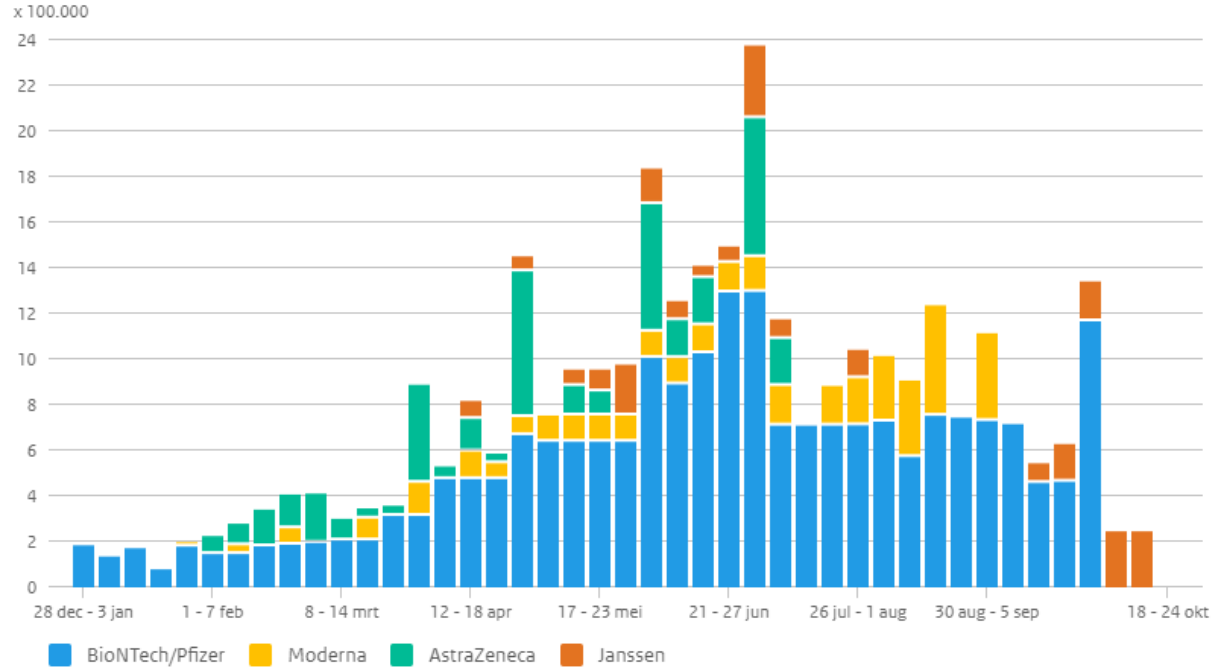

Figure 3: Provided COVID-19 vaccines during the first 9 months of 2021 in the Netherlands. The various vaccines provided show an estimate, as the later timepoints are not as up to date as they were during April-September 2021. Adapted from RIVM, CoronaDashboard 2021.

In healthy vaccinees, full AstraZeneca vaccination showed significantly lower IgG levels, compared to other vaccines, where the combination of 1 AstraZeneca and 1 Pfizer vaccination, showed similar IgG levels to vaccinees with a full Pfizer vaccination (Stefanski et al., 2021).
Due to the fact that RA is treated with various immunosuppressive drugs, the humoral response after contact with or vaccination for COVID-19 may be affected, as could be seen with prior viruses and other autoimmune diseases (Boekel et al., 2021; Hua et al., 2014; Nguyen et al., 2021). Some studies show that various drugs can influence the ability to develop antibodies postvaccination, while others only see the effect in RTX treated patients (Deepak, Kim & Paley, 2021; Spiera, Jinich & Jannat-Khah, 2021). The differences in serological levels were mainly seen after the first vaccination, with a similar level after the second vaccination. Boekel et al., performed a comparison study, including rheumatic diseases as well as participants with multiple sclerosis. The study found that after the first COVID-19 vaccination, participants that follow a therapy with MTX or anti-CD20 therapies show lower seroconversion rates than healthy controls and those without immunosuppressive medication. It was also found that participants with prior

SARS-CoV-2 infection showed similar serological levels after just one dose of the vaccination and patients without prior infection, but with two doses. Levels after the second vaccination, are similar within the therapy group and healthy controls (Boekel et al., 2021). These findings are similar to other studies. The study by Kennedy et al. in patients with inflammatory bowel disease and a TNF inhibitor shows a similar trend in seroconversion levels after prior SARS-CoV-2 infections and one dose, compared to patients with two doses and no prior infection (Kennedy, Lin, Goodhand, 2021). A different study by Haberman et al. in patients on MTX therapy also showed a lower seroconversion rate after the second vaccination (Haberman, Herati & Simon, 2021). The differences between these two studies may be due to the collection time of the samples post-vaccination, where the Boekel study obtained these in a median time of 38 days, compared to 7 days of the Haberman study. In healthy individuals, antibodies could be measured four to 15 days after the onset of symptoms (Post et al., 2020). Due to the delayed seroconversion rates in RA patients, it is suggested that treatment with MTX is likely to delay the development of humoral immunity in autoimmune diseases. The Haberman study also showed a decrease in activated CD8 T cells in patients undergoing MTX therapy, compared to healthy controls.

A study in France was started in October 2019 that observes patients treated with JAK inhibitors for inflammatory rheumatism (MAJIK), which includes rheumatoid arthritis as well as patients with psoriatic arthritis. This study allows researchers to assess serological values across France and the whole demographic. Seror et al. report findings from patients within the cohort that had a serological assessment at least two weeks post their final vaccination. 88% of the participating cohort showed an overall response rate to the vaccination while being treated with JAK inhibitors (Seror et al., 2022).

The beforementioned studies focus on humoral immunity, looking at serological values of IgGs. Apart from humoral immunity, cellular immunity also plays a role in vaccinations. Cellular immunity allows memory cells to be developed, allowing the system to attack a later infection with the virus. In combatting viral infections, cellular immunity is crucial. Circulating antibodies, remnants from the humoral immune response, may be short-lived, with a decrease of immunity after the infection (Liu et al., 2020).

As shown in figure 2, the B cell response plays a big role in the response against adenovirus vaccines. This raises the suspicion that the immune response in the population using therapy against B cells will have a reduced effect on the vaccination. The vaccine developed by Moderna showed a T cell response, accompanied by a neutralizing activity of the SARS-CoV-2 infection in the nose and lung, after two immunizations (Anderson et al., 2020; DiPiazza, Graham, & Ruckwardt, 2021). Similar results were found after two immunizations of the Pfizer vaccine. Adenovirus vector-based recombinant vaccine of AstraZeneca also showed an increased T cell response, with no clear differences between the one- or two-dosed groups (Folegatti et al., 2020). The 2021 study by Benucci et al, looked into RA patients that received RTX therapy in varying time frames (6, 9 and 12 months) prior to vaccination with the Pfizer mRNA vaccine. However, this study only concluded 14 patients, 4, 5 and 5 patients per group, respectively. Despite the B cell depletion activity of RTX, a T cell immune response was still seen, despite the absence of B lymphocytes (Benucci et al., 2021). The 2021 study in Germany by Stefanski et al, looked into, among others, patients undergoing RTX therapy for RA and RA patients undergoing different therapy. Peripheral blood samples were collected after full vaccination of Pfizer, Moderna or AstraZeneca vaccines, or the combination of 1 AstraZeneca vaccination followed by 1 Pfizer vaccination. The RTX patients had their last treatment at a median of 9 months prior. Compared to healthy controls, RA and RTX patients showed a significantly lower and delayed response in antibody formation. The study also showed that patients undergoing RTX therapy were subject to a lower amount of antigen-specific B cells, reduced activation of CD4/8 T cells and diminished circulating TfH-like CD4 T cells (Stefanski et al., 2021). Mrak et al (2021), also investigated the role of RTX in immune response post SARS-CoV-2 vaccination. The patients were either vaccinated twice with the Moderna or Pfizer vaccine and the samples were obtained at a mean

of 21 days. In the RTX patients it was found that despite the limited number of B cells, there was still a T cell mediated immune response upon vaccination (Mrak et al., 2021).
Currently, many countries offer an additional vaccination time point, referred to as the booster. This booster is given to increase immune responses and allow a better response to new variants (Shekhar et al., 2021). However, for immunocompromised people, the booster would be the fourth injection, compared to the third injection in healthy individuals. The third injection for immunocompromised people is used to complete the regular vaccination program, due to the lessened immune response shown in patients that follow therapies affecting the immune responses. However, due to the fact vaccinations have not been readily available for long and the concerns patients may have, not many patients have received the third injection, or have been given the opportunity to join studies investigating the immune response obtained by this third injection. A study by Felten et al. was published in early January 2022, investigating the cellular and humoral immunity after the third dose in patients that were treated with rituximab. However, this study only considers 10 RTX patients, which allows an idea, rather than a solid theory on the effects. The participants received the third dose a month after the second injection. Felten hypothesizes that this month is too little for complete B cell repopulation, which would allow an increased immune response as no differences were shown in the serological values after two or three doses (Felten, 2022).

5. Discussion.

In the midst of the current pandemic, it is important to know how to, safely, battle COVID-19. Not only for healthy individuals, with no underlying diseases but especially for immunocompromised individuals. This review focused on the relation between RA and the influence the provided therapies could have on SARS-CoV-2 vaccination. As the RA therapies influence various immune responses, it is likely that vaccination for SARS-CoV-2 could be impaired. However, due to the novelty of the SARS-CoV-2 virus and the COVID-19 disease, limitations are encountered in the search for the answer to the safety and efficacy of the various available vaccination. The studies describing the various immunological responses are limited in size and knowledge. Many studies struggle to find a coherent cohort of disease and healthy controls. Especially the vast number of varying therapies available to RA yields an incoherent view, as these varying drugs have different effects on the immune responses. It is known that RA patients do not have the same immune response as healthy controls after vaccination, as seen for Hepatitis B vaccination (Intongkam et al., 2019) and various viruses, including herpes zoster (Meroni, Zavaglia & Girmenia, 2018).

Therapy based on broad-spectrum immune suppression, including MTX, RTX and JAKinibs are linked to worse outcomes when encountering COVID-19, compared to healthy controls. However, patients undergoing therapy where specific immune pathways are dampened, seem to have a sufficient immune response (Fagni et al., 2021). Various studies showed the importance of the humoral immune response in the light of vaccine effectivity (Boekel et al., 2021; Deepak et al., 2021; Seror et al., 2022; Stefanski et al., 2021). A common therapy used for RA patients is MTX. Studies have shown that patients undergoing MTX therapy have a reduced number of antibodies, compared to healthy controls (Fagni et al., 2021). RTX, a drug often given in combination with MTX, shows an impaired B cell response, as it is a B cell depleting drug. Interestingly, the T cell response within RTX patients appears to be comparable to healthy controls, showing an effective response. Not a lot is known yet about the effectiveness of the third dose of vaccination. Studies show the humoral response is slightly increased in comparison to a two-dose vaccination. No differences were noted in the number of B cells present in the serum, hence not yielding a very significant difference. Suggestions were made to increase the time between retrieving the second and the third dose, to increase the number of B cells naturally. The studies mentioned in this review have various limitations, including the number of participants. This leads to a small cohort, which can influence the outcomes of the results. In further research, it is important to increase the cohort size. Another possibility would be to combine the data from various studies, to form one larger cohort. This is likely to show more coherent and significant results, compared to studies with only a cohort of seven to twelve RA patients.

It is also interesting to note that various RA therapies, including baricitinib, are used in hospitals to treat COVID-19 patients. These therapies allow a reduction in inflammation in these patients.

Despite the impaired immunological response directly after vaccination, results show that RA patients do have a sufficient immune response to the COVID-19 vaccination. Therefore, it can be said that RA patients can safely and effectively obtain protection after the COVID-19 vaccination.

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