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Updated recommendations of the German Society for Rheumatology for the care of patients with inflammatory rheumatic diseases in the context of the SARS-CoV-2/COVID-19 pandemic, including recommendations for COVID-19 vaccination

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Supplementary Information

The online version of this article (<https://doi.org/10.1007/s00393-021-01055-7>) contains a summary of these recommendations composed for patients.

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All authors are writing on behalf of the Executive Board of the German Society for Rheumatology



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Core recommendations

■ Table 1.

1 Introduction

Even after more than one year, the COVID-19 pandemic is a great challenge for patients with inflammatory rheumatic diseases (IRD) as well as for rheumatologists. The recommendations of the German Society for Rheumatology (Deutsche Gesellschaft für Rheumatologie e. V.; DGRh) of March 2020 were intended to provide initial, rapid guidance on specific concerns in the care of patients with IRD in the face of the threat posed by SARS-CoV-2. These were based primarily on expert consensus [1–3]. The first update in July 2020 [4, 5] already relied on scientific data from registries, cross-sectional studies, case reports, and case series [6, 7]. In the meantime, we have further results from scientific publications on COVID-19 in IRD, from which much

more precise statements on disease- or therapy-related risks can be derived. An important reason for updating the recommendations for action again is the fact that vaccinations against SARS-CoV-2 are now available and are thus increasingly being administered to patients with IRD. This raises many questions, also and especially for patients with IRD, but also for the physicians and medical professionals caring for them.

2 To whom should these recommendations apply?

The statements and recommendations made here refer to patients with inflammatory rheumatic diseases (IRD), especially in consideration of the medicinal antirheumatic therapy. Where appropriate or necessary, comparisons are also made with SARS-CoV-2 infections and COVID-19 in the general population. The statements have to be relativised—at least partially—for IRD patients who have

Empfehlungen und Stellungnahmen von Fachgesellschaften

Table 1 Core recommendations of the DGRh for the care of patients with inflammatory rheumatic diseases in the context of the SARS-CoV-2/COVID-19 pandemic			
#	Recommendation	LoA ^a (± SD)	GoR
1	Patients with inflammatory rheumatic diseases (IRD) should follow the behavioural and precautionary measures described by the Robert Koch Institute to avoid infections. This also applies in the case of a positive SARS-CoV-2 IgG antibody detection. Special additional measures are not necessary	9.9 (± 0.43)	↑
2	To interrupt chains of infection and contain a new possible wave of infection, patients may be advised to use the “Corona Warning App” or similar digital applications	8.95 (± 1.25)	↔
3	The individual risk for infection or severe disease progression can be estimated based on general (such as age, multimorbidity, obesity, smoking) and disease-specific (e.g. high activity of IRD, severe systemic disease) risk factors	9.43 (± 0.85)	↑↑
4	Initiation or change of antirheumatic therapies should neither be omitted nor delayed due to the COVID-19 pandemic	9.9 (± 0.43)	↑↑
5	Before administering rituximab, an individual risk–benefit assessment should be carried out due to the increased risk of a severe COVID-19 course, and the use of alternative therapies should also be examined	9.81 (± 0.5)	↑
6	In patients without signs of infection, even with contact with SARS-CoV-2 positive persons, the existing antirheumatic therapy should be continued unchanged. This also applies to the therapy with glucocorticoids in the therapeutically necessary dose	9.76 (± 0.53)	↑
7	In patients tested positive for SARS-CoV-2 by PCR without signs of infection, pausing or delaying ts- or b-DMARD therapy for the duration of the mean incubation period of SARS-CoV-2 infection (e.g. 5–6 days) should be considered. Generally, csDMARDs should not be discontinued in the absence of signs of infection	9.38 (± 0.72)	↑
8	In patients with confirmed active COVID-19, DMARD therapy should be paused and leflunomide washed out if necessary. Continuous GC therapy ≤ 10 mg/day used for the treatment of the rheumatological disease should be continued at the same dose	9.43 (± 0.85)	↑
9	Rheumatologists should always be involved in the decision to maintain, reduce or pause antirheumatic therapy in the context of COVID-19	9.89 (± 0.31)	↑
10	A general recommendation for screening patients with IRD for SARS-CoV-2 antibodies after infection cannot be given at present due to a lack of data on antibody formation and persistence (especially under immunosuppression)	9.33 (± 1.21)	↑
11	Patients with IRD and positive test for SARS-CoV-2 (PCR, rapid antigen test, antibody test) should be documented in the COVID-19 registry of the DGRh (COVID19-rheuma.de)	9.76 (± 0.61)	↑
12	Patients with IRD should be vaccinated against SARS-CoV-2 following the vaccination recommendations of the STIKO	10 (± 0)	↑↑
13	The presence of IRD alone does not imply a preference for one of the vaccines approved in Europe. With the aim of rapid immunisation in urgently needed rituximab therapy and in patients over 60 years of age with confirmed APS or immune thrombocytopenia, the use of an mRNA vaccine should be considered as a precaution in these situations	9.48 (± 0.85)	↑
14	General discontinuation of DMARD therapy solely due to vaccination—as DMARDs and immunosuppressants can attenuate the measurable humoral immune response after COVID vaccination (with this most clearly affecting rituximab and least affecting anti-cytokine biologics)—is not recommended, as it is not known to what extent this affects actual vaccination protection	9.71 (± 0.55)	↑↑
15	Pausing methotrexate for 1–2 weeks after each vaccination, JAK inhibitors for 1–2 days before and 1 week after each vaccination, and abatacept for 1 week before and after each vaccination can be considered if IRD is in stable remission. But this is not mandatory. Good disease control has priority over a possibly attenuated immune response, even in the context of vaccination	9.1 (± 0.92)	↔
16	The vaccination series should begin at least 4 months after the last rituximab administration and rituximab should ideally be given at the earliest 4 weeks after completion of the vaccination series. In individual cases and patients at risk, this may be deviated from	9.29 (± 0.93)	↑
17	SARS-CoV-2 antibody titres should not be determined regularly to monitor vaccination success. It is not yet clear to what extent the results are predictive of protection against infection or disease	9.48 (± 0.79)	↑

^aLoA Level of Agreement (± standard deviation) after consultation in the author group with 21/21 votes for every item. GoR Grade of recommendation. ↑↑ strong recommendation, ↑ recommendation, ↔ open recommendation (according to 3-level grading of the AWMF regulations). Although level 2b or 3b evidence was also available for individual recommendations, only evidence level (LoE) 5 is used for the consensus recommendations and is not shown individually in the table
 APS antiphospholipid syndrome

Table 2 General risk factors for a severe course of COVID-19

Higher age
Male gender
Smoking
Obesity
Multimorbidity, especially pre-existing lung disease, renal insufficiency, diabetes mellitus, hypertension, coronary heart disease

been vaccinated against COVID-19 or who are protected after a SARS-CoV-2 infection. However, there is still no clarity as to whether and how a vaccination's success or protection after a previous infection can be investigated with sufficient reliability and when booster vaccinations may be necessary. It should also be pointed out that these recommendations cannot cover all situations that justify or even suggest a deviation from them in individual cases.

3 What is the risk for patients with IRD for infection with SARS-CoV-2 and a severe course of COVID-19?

An idea of the significance of age for the risk of COVID-19 for hospitalisation and death, also in relation to various concomitant diseases, is given in **Fig. 1** in the appendix from a comprehensive so-called "Umbrella Review" of the Robert Koch Institute (RKI) [8].

3.1 General risk factors for COVID-19 and a severe course

Risk factors in the general population for a severe course of COVID-19 (**Table 2**; [9]) also apply to patients with IRD [10–20].

3.2 Specific risk factors of inflammatory rheumatic diseases for SARS-CoV-2 infection and severe course of COVID-19

3.2.1 Risk for infection

Whether patients with IRD have an increased risk of COVID-19 compared to the normal population is not conclusive. While some studies report an increased risk of COVID-19 compared to the normal population or compared to a "matched" population without IRD in certain patient popula-

tions, e.g. in patients with systemic sclerosis [20–22], others indicate a comparable risk to the normal population [23–25].

3.2.2 Risk of a severe course

Current data from registries and a meta-analysis [20] mostly confirm results from early case series [26], according to which the risk of a severe course (defined here and in the following as inpatient admission and/or the need for ventilation and/or death) is generally not increased in patients with IRD in total compared to the normal population or compared to "matched" cohorts without IRD. As in the normal population, the risk is increased above all in the presence of comorbidities [12–15, 27]. Only a few cohort studies found an enhanced risk for a severe course in patients with rheumatoid arthritis [28, 29] or in the total cohort of IRD patients compared to the normal population or to "matched" cohorts without IRD. These publications show a high proportion of patients with connective tissue disease and vasculitides (**Table 5** in the appendix), which could possibly contribute to a more severe course (see [28]). Subgroup analyses from recent registry and cohort studies support this finding: systemic diseases such as vasculitides, SLE, systemic sclerosis, Sjögren's syndrome, as well as autoinflammatory diseases possibly carry a higher risk for a severe COVID-19 course or death compared to the normal population or a matched non-IRD population or rheumatoid arthritis used as a reference [12, 13, 18, 19, 28–30]. When interpreting these data and drawing conclusions from them, it must be taken into account that only relatively small numbers of cases of these IRD subpopulations have been recorded in the registries and cohort studies to date. It is also unclear whether the increased risk for a severe course is caused by the disease itself or by certain organ involvement (e.g. lung or kidney involvement) or the intensity of immunosuppression.

In analyses from the German and global COVID-19 registries, high disease activity of the respective IRD was clearly identified as a risk factor for a severe course of COVID-19, with an odds ratio (OR) of 1.96 (95% confidence interval [CI] 1.02–3.76) and 1.87 (95% CI 1.27–2.77), respectively, compared

to patients with low or no disease activity [14, 15].

4 Influence of immunosuppressive/immunomodulatory drugs on the course of COVID-19

4.1 Glucocorticoids

Long-term therapy with glucocorticoids (GC) is a known risk factor for infections and also for a more severe course of infections in IRD [31, 32]. Cohort studies and registry data have shown that this also applies to COVID-19: Therapy with GC was already associated with an increased COVID-19 infection rate from a dose of 2.5 mg daily in a large northern Italian cross-sectional study of over 2000 IRD patients [33]. GC use at doses of 10 mg (prednisone equivalent) daily and above resulted in an increased risk of severe COVID-19 compared with a matched non-IRD population at an OR of 1.97 (95%CI 1.09–3.54) in a cohort study of 694 patients with IRD [13]. In the global registry study of 3729 IRD patients, the OR for COVID-19-associated mortality was 1.7 (95%CI 1.18–2.41) for GC above 10 mg daily versus no systemic GC intake [15]. In the German registry of 468 IRD patients, the OR for GC > 5 mg was 3.67 (95%CI 1.49–9.05) versus no glucocorticoid therapy [6].

The interpretation of this risk increase must be made with caution since an increase in the glucocorticoid dose in most cases occurs due to increased disease activity leading to "confounding by indication". In a further evaluation of the global registry, it could be shown that in remission or low disease activity, even GC in a dosage of > 10 mg daily versus no glucocorticoid therapy are not associated with a higher risk of a more severe course or death [34]. Therefore, the data suggest that higher disease activity is the main risk factor compared to the GC dose, but since the strength of the association with a more severe course within the subgroups of different disease activity increased with higher GC doses, it cannot be ruled out that GC exert an additional negative influence.

4.2 Conventional DMARDs¹, immunosuppressants, and immunomodulators

In the analysis of the global IRD registry with data up to July 2020, ongoing therapy with immunosuppressants overall (azathioprine, cyclophosphamide, ciclosporin, mycophenolate, tacrolimus) was significantly associated with a lethal outcome of COVID-19 with an OR of 2.22 (95%CI 1.43–3.46), as was therapy with sulfasalazine with an OR of 3.6 (95%CI 1.7–7.8) [15]. In the French registry, of the immunosuppressants, mycophenolate was conspicuous for a severe course (ventilation or death) with an OR of 6.6 (95%CI 1.47–29.6), while no signal was found for methotrexate, leflunomide, and azathioprine (although the number of cases for azathioprine was very small) [13]. In the evaluation of the global registry, “no DMARD therapy” was also associated with an increased OR for a lethal course of 2.11 (95%CI 1.48–3.01) compared to methotrexate monotherapy. In the aforementioned northern Italian cohort study, there was no increased risk of COVID-19 infection either in the group of conventional synthetic DMARDs (csDMARDs) or in the group of biological or targeted DMARDs (b/tsDMARDs), although an analysis by individual substances was not carried out [33].

4.3 Biologics and JAK inhibitors

There is increasing evidence that B-cell depletion, or possibly only significant hypogammaglobulinemia, are risk factors for a severe course of COVID-19. Initially, individual cases were reported [35–38] of a more severe course of COVID-19 after or during therapy with rituximab. Rituximab therapy was significantly associated with a fatal course of COVID-19 in the global COVID-19 registry on IRD [15] with an OR of 4.04 (95%CI 2.32–7.03) and in the French registry [13] with an OR of

4.21 (95%CI 1.61–11.0). In another analysis of the French registry [39], a total of 137 (13%) severe courses and 89 (8%) deaths were found in 1090 patients with IRD (mean age 55 ± 16 years; 734 [67%] female). Of 63 patients treated with rituximab, 13 (21%) died compared to 76 (7%) of the 1027 patients without rituximab. Although the risk of death adjusted for the above-mentioned parameters was not significantly increased in the rituximab group (effect size 1.32, 95% CI 0.55–3.19, $p=0.53$), severe courses were significantly more frequent with rituximab ($n=22$) than in the control group ($n=115$), even after adjustment (effect size 3.26, 95% CI 1.66–6.40, $p=0.0006$).

The Global Rheumatology Alliance (GRA) evaluated 2869 of 6132 RA patients in the global COVID-19 registry (as of mid-April 2021) who were on treatment with the biologics abatacept ($n=237$), rituximab ($n=364$), IL-6R inhibitors ($n=317$), TNF inhibitors ($n=1388$) or JAK inhibitors ($n=563$) at the time of infection. A higher rate of treatment with TNF and IL-6R inhibitors was found in nonhospitalised RA patients and a higher rate of treatment with rituximab in oxygen-dependent and deceased RA patients; the rate of treatment with JAK inhibitors was also slightly higher. In multivariate analysis adjusted for age, sex, region, season, obesity, smoking, csDMARDs, GC (\pm /dose), disease activity and the number of comorbidities, the OR for a severe course of COVID-19 versus treatment with TNF inhibitors was 4.15 (3.16–5.44) for rituximab and 2.06 (1.60–2.65) for the JAK inhibitor group [40]. Whether a protective effect of TNF or IL-6R inhibitors concerning severe courses of COVID-19 may also play a role here cannot yet be answered. Patients under TNF inhibitors were chosen as a reference in the multivariate analysis, and patients under IL-6R inhibitors did not show any difference. It should be mentioned, however, that even among the 571 patients treated with TNF blockers in the German registry so far, only two fatal courses of COVID-19 were recorded and the number of hospitalised cases was comparatively low at 52 patients (as of 23 May 2021). However, it must be taken into account that patients treated with TNF inhibitors were on average younger (53 vs. 59 years),

received GC less frequently, and had less disease activity compared to patients not treated with TNF blockers.

In summary, due to an increased risk of a more severe course of COVID-19 during therapy with rituximab, we recommend that this therapy be carefully weighed up about possible alternatives or concerning the individual benefit and risk. Otherwise, the risk of increased disease activity for a severe course of COVID-19 is estimated to be higher than the risk of a severe course due to antirheumatic therapy. It is therefore not recommended to discontinue or reduce antirheumatic therapy as a precaution. Even a therapeutically necessary glucocorticoid dose should not be changed out of concern for a more severe course of COVID-19.

5 Prevention of infections and protective measures

Common behavioural and precautionary measures described and regularly updated by the Robert Koch Institute [41] and the Federal Centre for Health Education [42] for the general population and for persons at special risk apply. Special measures going beyond this are not recommended.

Weighing up the benefits and risks, there is no need to avoid visits to the doctor intending to reduce the risk of infection. Necessary inpatient treatment should not be delayed.

Appropriate behavioural and hygienic measures must continue to be ensured in out- and in-patient settings. Intelligent planning of consultation hours should be carried out (e.g. short waiting times, observance of distance rules, wearing of mouth and nose protection masks, minimisation of the number of accompanying persons, generous ventilation).

To prevent the spread of infection, patients should be informed in advance not to attend unannounced health facilities with symptoms of illness or after contact with people who are known to be infected with SARS-CoV-2. In such cases or after a stay in a high-risk or virus variant area (“variants of concern”), the practice should first be contacted by telephone.

Typical COVID-19 symptoms (see **Table 6** in the appendix) or contacts to infected persons can be asked for in

¹ The term Disease modifying antirheumatic drug (DMARD) is usually used only in the context of inflammatory joint diseases. In these recommendations, for simplicity, it is used for the drug groups regardless of the respective indication.

advance. In case of doubt, adequate testing is recommended. To break chains of infection and contain new possible waves of infection, patients can be advised to use the “Corona warning app” or comparable digital applications [43].

According to the recommendations of the Standing Commission on Vaccination (STIKO) of the Robert-Koch-Institute (RKI), the vaccination status should be updated: In addition to SARS-CoV-2 (see section 8), this primarily concerns vaccinations against pneumococci and influenza.

6 Antirheumatic therapy in the context of SARS-CoV-2 or COVID-19

In principle, rheumatologists should always be involved in the decision to maintain, reduce or pause antirheumatic therapy in the context of COVID-19. Counseling regarding antirheumatic therapy should be performed in a shared-decision manner between doctor and patient even in the context of the COVID-19 pandemic. To further improve the data situation, it is recommended that patients with IRD and COVID-19 (detected through positive PCR, rapid antigen test, or antibody test for SARS-CoV-2) are documented in the COVID-19 register of the DGRh (COVID19-rheuma.de).

The following specific recommendations continue to apply:

6.1 Patients without signs of infection

6.1.1 Existing antirheumatic therapy

– Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (GCs), conventional synthetic DMARDs (csDMARDs), targeted synthetic DMARDs (tsDMARDs), biologic DMARDs (bDMARDs) and immunosuppressants (see section 4.2) should be continued unchanged as indicated by the IRD and should not be discontinued or reduced for fear of SARS-CoV-2 infection alone. The GC dose should be kept as low as possible—as is valid for all situations in IRD therapy—and a necessary increase above 10 mg daily should be accompanied by consistent protective measures.

– In the case of therapy with rituximab (RTX) in indications without potentially life-threatening manifestations, especially in uncomplicated RA in sustained remission, a postponement of RTX administration should be considered, also to enable a potentially more promising vaccination of the patient (see section 8). This should be done after weighing the risk of relapse against the individual risk of infection. Under no circumstances should the use of RTX for remission induction be delayed in cases of systemic diseases that pose a serious threat, e.g. ANCA-associated vasculitis (AAV).

6.1.2 Restarting or changing antirheumatic therapy

– The start of antirheumatic therapy should not be omitted or delayed because of the COVID-19 pandemic; the dose should follow the usual recommendations.

– A recommendation for or against a specific DMARD (for RTX see next point in the list) cannot currently be made for new patients.

– In the case of valid alternatives (e.g. in RA), the use of RTX should be critically questioned because of possible favouring a more severe course of COVID-19 (see section 4.3), the long B-cell depletion, and limited vaccination response. However, the use of RTX for remission induction in systemic diseases (e.g. in AAV) should not be omitted in concern of COVID-19.

– Protocols with reduced GC administration, e.g. in giant cell arteritis or AAV should be preferred [44, 45].

6.2 Patients with contact to SARS-CoV-2 positive persons and without own COVID-19 infection signs

– The therapy should be continued as described in section 6.1. If symptoms occur, a doctor or rheumatologist should be contacted (see section 6.3).

6.3 Patients with signs of infection after contact with SARS-CoV-2 positive persons

– A change in therapy should not be made if symptoms are mild and fever is absent.

– If there are clear signs of infection and especially fever (> 38 °C), the antirheumatic medication should be paused.

– GC therapy ≤ 10 mg prednisolone equivalent daily can be continued; for higher doses, the continuation of GC treatment must be decided on an individual basis.

6.4 Patients tested positive for SARS-CoV-2 and without signs of COVID-19 infection

– Pausing or delaying ts- or bDMARD therapy for the duration of the mean incubation period may be considered. As it is often not known when an infection has occurred, a pause for 5–6 days after smear may be considered if symptom-free conditions persist.

– GC therapy ≤ 10 mg prednisolone equivalent daily can be continued; at higher doses, the continuation of GC treatment must be decided on an individual basis.

– csDMARDs should not be discontinued.

6.5 Patients tested positive for SARS-CoV-2 and with signs of COVID-19 infection

– GC therapy ≤ 10 mg prednisolone equivalent daily can be continued; for higher doses, the continuation of GC treatment must be decided individually.

– DMARDs should be paused in this situation (leflunomide should be washed out, if necessary, because of the long half-life of this compound).

– In patients at risk for severe COVID-19 progression (e.g. severe immunosuppression with active IRD, primary immunodeficiencies), early passive immunisation with a combination of two neutralising monoclonal antibodies should be considered according to the COVRIIN/STAKOB/DGI statement

Company	Name	Vaccination type	Doses	Schedule	Application	EU approval
BioNTech/Pfizer	Comirnaty® (BNT162b2)	mRNA + LNP	2	Days 0, 21/6 weeks ^a	i.m.	21 Dec. 2020
Moderna	COVID-19-Vaccine Moderna (mRNA-1273)	mRNA + LNP	2	Days 0, 28/6 weeks ^a	i.m.	06 Jan. 2021
Astra-Zeneca/Oxford University	Vaxzevria® (AZD1222)	Vector-based ChAdOx1, nonreplicative	2	Days 0, 28–84/12 weeks ^a	i.m.	29 Jan. 2021
Janssen-Cilag International N.V.	Ad26.COV2.S	Adenovirus-26-Vector-based, nonreplicative	1	Single shot	i.m.	11 Mar. 2021

^aRecommendation of the STIKO regarding the scheduling of the second vaccination [49]

(for current information including link to the list of therapy centres see [46] or explanation in the supplementary online information).

7 Proof of past infection with SARS-CoV-2

With the duration of the pandemic, the proportion of patients who have been exposed to SARS-CoV-2 increases, regardless of whether COVID-19 symptoms were present. In the future, it may become important to be able to estimate the individual risk of infection by knowing the patients' (possibly protective) immune status against SARS-CoV-2. At present, due to lack of data on antibody formation and persistence and the importance of T-cell immunity, especially under immunosuppression, and due to limited or unclear specificity and sensitivity of the different test methods, no recommendation can yet be made for screening patients with IRD for antibodies. A general screening before vaccination in the absence of clinical evidence of a previous infection is not recommended.

Furthermore, it cannot be assessed at present whether the risk of re-infection or contagiousness is reduced if IgG antibodies against SARS-CoV-2 are detected. Thus, even in the case of a positive antibody test, it is not recommended to loosen the measures for infection and foreign infection prophylaxis.

8 Vaccination against COVID-19

8.1 Introduction

Despite worldwide efforts to develop effective drugs for the treatment of COVID-19, there is as yet no therapeutic option

that promises a cure with sufficient certainty. Thus, vaccination of large parts of the population as soon as possible is considered the decisive step to contain the pandemic [47].

Also for the accelerated assessment and approval procedures of the COVID-19 vaccines by the EMA, the safety standards required for approval applied without restriction [48]. Currently, four SARS-CoV-2 vaccines are available in Germany [49]. These are two messenger RNA (mRNA) vaccines and two vector vaccines (■ Table 3).

Patients with known or suspected immune dysfunction were excluded from the phase III trials of the vaccines, but because "healthy adults and those with stable pre-existing conditions" could be included [8], the pivotal trials with more than 43,000 [50] and more than 30,000 [51] subjects included also some with IRD [25].

Based on this situation, the DGRh had published the first recommendations for vaccination of patients with IRD or under immunomodulating therapies against SARS-CoV-2 in IRD and subsequently updated them (online) several times. These recommendations could not be based on studies on the safety and efficacy of SARS-CoV-2 vaccines in IRD patients so far but were consented based on findings with other vaccinations in IRD patients among the experts of the COVID-19 commission of the DGRh [52–54]. In addition to a continuous literature search, national [8, 47, 49] and international recommendations of other professional societies [55, 56] were also taken into account.

8.2 Type of vaccines and inflammatory rheumatic diseases

None of the vaccines against SARS-CoV-2 approved so far is a live vaccine. Therefore,

all of them can be administered to patients with IRD, even under immunosuppressive/immunomodulatory therapy. Apart from extremely rare allergies to vaccine components, there are no contraindications to COVID-19 vaccination.

8.3 Vaccination against COVID-19 during pregnancy and lactation

From an ongoing study of more than 35,000 pregnant women vaccinated against COVID-19 with mRNA vaccines, a first interim evaluation of 827 completed pregnancies was carried out, in which no significant safety signals were seen [57]. The STIKO does not currently make a general vaccination recommendation for pregnant women. Pregnant women with previous illnesses and a resulting high risk of severe COVID-19 disease or with an increased risk of exposure due to their life circumstances can be offered vaccination with an mRNA vaccine from the 2nd trimester onwards after a risk–benefit assessment and detailed medical information [49]. The German Society for Gynaecology and Obstetrics recommends (as of 05/2021) that pregnant women are vaccinated with mRNA-based vaccine against COVID-19 in an informed participatory decision-making process and after exclusion of general contraindications [58]. To protect pregnant women indirectly, the prioritised vaccination of close contacts of pregnant women, especially their partners, as well as midwives and doctors, is also recommended. mRNA-based vaccination against COVID-19 should be offered and made available to breastfeeding women.

8.4 Are there differences in the effectiveness of COVID-19 vaccines?

The vaccines approved in Germany by BioNTech/Pfizer, Moderna, AstraZeneca, and Janssen (Johnson & Johnson) all offer protection against symptomatic infections. The efficiency data in the prevention of all infections determined by the clinical trials as percentages only reflect the effectiveness to a limited extent. All vaccines approved to date can largely prevent severe courses and deaths [49]. Current data on the vaccines can be found on the website of the Paul Ehrlich Institute (PEI) (<https://www.pei.de/DE/arzneimittel/impfstoffe/covid-19/covid-19-node.html>).

8.5 Efficacy of vaccines against SARS-CoV-2 variants

All vaccines licensed in Europe are considered to provide very good protection against symptomatic disease not only against the original “wild type” of SARS-CoV-2 but also against the alpha (B.1.1.7) and delta (B.1.617.2) variants currently prevalent in Germany, although a complete vaccination series seems to be important for protection against the delta variant [49].

8.6 To what extent does an inflammatory rheumatic disease or immunosuppressive/modulatory therapy change the entitlement to COVID-19 vaccination?

According to the Corona Vaccination Ordinance (CoronalmpfV) of the Federal Ministry of Health, patients with rheumatic diseases have so far been entitled to be vaccinated with increased priority, and in the case of certain organ manifestations also with high priority [59]. Concerning changes or cessation of prioritisation, reference is made to the current Corona Vaccination Ordinance in the official “Bundesanzeiger”, the recommendations of the Robert Koch Institute, and the website of the DGRh. Even if prioritisation is discontinued, the DGRh would like to point out that patients with IRD should continue to be vaccinated preferentially.

8.7 Tolerance of vaccinations in rheumatic diseases

On the question of the tolerability of COVID-19 vaccinations in patients with IRD, an online survey of 325 patients [60] and two first prospective German studies with 29 and 84 patients [61, 62] have been published so far. Overall, good tolerability and no specific intolerance reactions were observed. However, only mRNA vaccines were used in all these studies. With more than 1.4 billion vaccinations administered worldwide (as of 15 May 2021) [63], there is currently no evidence that patients with IRD have a different spectrum of side effects or increased adverse reactions to the currently approved vaccines than the normal population. In principle, there is a recommendation not to administer elective vaccinations during a disease flare, but whether vaccination against COVID-19 should be made at all dependent on actual disease activity is controversial [55, 56].

8.8 Can COVID-19 vaccination trigger a flare of rheumatic diseases?

Theoretically, vaccines, like infections, could trigger relapses of known or even initial manifestations of IRD. This is not yet known for the currently approved vaccines against COVID-19. According to current knowledge, the benefit of vaccination clearly outweighs the theoretical risk of a usually only slight or temporary activation of the underlying disease. Studies on other vaccines showed no evidence that they trigger flares of IRD [64, 65]. In the first German study mentioned above, no effect on the activity of the underlying disease was found in association with the mRNA vaccination against SARS-CoV-2 [61]. Even if in individual cases “relapses” can occur in the context of the (desired) vaccination response, which can generally be controlled with symptomatic therapy, there are no hints for permanent activation of an IRD by vaccination against SARS-CoV-2. Therefore, concerns about the worsening of an IRD are no reason to refrain from vaccination.

8.9 Is there a vaccine to prefer for rheumatic diseases or immunomodulatory medication?

The STIKO does not derive any preference for a specific vaccine for the German population from the data available to date on the effectiveness of the available vaccines with regard to the virus variants known to date but assumes that all vaccines available to date are equally suitable for combating the pandemic [49].

No significant differences in the safety of these vaccines can be inferred from the controlled trials. Postmarketing surveillance for the AstraZeneca vaccine showed evidence of very rare immunologically mediated events, predominantly in younger female patients with thrombocytopenia, coagulation disorders, and unusual thromboses, including sinus vein thrombosis [66–68]. The EMA sees a probable connection with the vaccine, but continues to assume a clearly positive benefit–risk ratio due to the rarity of the events and has therefore not decided on any restrictions on the use of the AstraZeneca vaccine [69]. For Germany, the PEI and the STIKO came to a different conclusion and recommend its use, as well as that of the Johnson & Johnson vector vaccine due to similar complications, only for people under 60 years of age after detailed medical information [49].

Comparative data on the efficacy and safety of the vaccines currently used in Germany in patients with IRD is not available. This means that beyond the general differences described and the restrictions on use imposed by the PEI and the STIKO, there is no preference for patients with IRD in favour of a particular vaccine.

For two patient groups with IRD, namely patients in whom rapid complete immunisation is indicated because of urgent therapy with RTX and patients over 60 years of age with confirmed APS (antiphospholipid syndrome) or immunothrombocytopenia, the administration of an mRNA vaccine is recommended as a precautionary measure in view of the DGRh.

The mechanism of the very rare coagulation disorders, thrombopenias, and sinus vein thromboses is probably based on the formation of autoantibodies (VIPI: vaccine-induced prothrombotic immune

thrombocytopenia) [66]. The postmarketing surveillance data from Great Britain show comparatively more reported cases of APS and ITP under vaccination with the AstraZeneca vaccine [70] than with the Pfizer/BioNTech vaccine [71], although the number of cases cannot be analysed with statistical certainty. However, details on the cases of VIPI that have occurred so far are hardly available. Among 9 published cases, 2 were patients with pre-existing autoimmune disease, including 1 with positive antiphospholipid antibodies [66]. In a Norwegian study of healthcare workers, antibodies to platelet factor 4 (PF4) were detected in 6/492 cases after vaccination with the AstraZeneca vaccine. None of these cases developed thrombopathy or thrombosis [72].

If this does not delay vaccination, for patients with confirmed APS or immunothrombocytopenia, the use of an mRNA vaccine could represent a risk reduction. This does not apply to cases where only low-titre or single antiphospholipid antibodies are detectable or where there is no chronic immunothrombocytopenia.

With the mRNA vaccines, immunisation can be achieved within about 4–7 weeks: Currently, based on modeling by the RKI and the available data, a vaccination interval of 6 weeks is recommended for the mRNA vaccines, and 12 weeks for the AstraZeneca vaccine [49]. Immunity exists 2 weeks after the second vaccination (BioNTec, Moderna, AstraZeneca) or after the single vaccination (Johnson & Johnson), according to the respective technical information. Patients for whom therapy with RTX is urgent would benefit from rapid immunisation, as a significantly reduced vaccination response can be assumed after such anti-B cell therapy over a longer period of time. Under ongoing therapy with RTX, e.g. for remission maintenance in AAV, there may only be short time windows in which vaccination appears promising—at least with regard to anti-body formation. In these cases, too, patients would benefit from the use of an mRNA vaccine. There are no concrete data available on this procedure for IRD either. There is only a plausible analogy to other vaccinations.

For both case constellations, the DGRh concludes that vaccination should also be carried out with vector vaccines if, e.g. for

reasons of availability, an mRNA vaccine cannot be used promptly, as the risk of a severe SARS-CoV-2 infection outweighs the possible vaccination risks.

8.10 Vaccinations following SARS-CoV-2 infection

Due to the immunity after a SARS-CoV-2 infection and because of the continuing vaccine shortage, immunocompromised persons who have undergone a SARS-CoV-2 infection confirmed by direct pathogen detection (PCR) should, in the opinion of the STIKO, receive a COVID-19 vaccination 6 months after recovery or diagnosis, taking into account prioritisation. Initially, one vaccine dose is sufficient for this, as high antibody concentrations can already be achieved, which cannot be further increased by a second vaccine dose. On the other hand, it must be decided on a case-by-case basis whether a single vaccination is sufficient or whether a complete vaccination series should be administered to persons with “impaired immune function” [49].

8.11 Is the effect of corona vaccination attenuated by antirheumatic therapy/ immunosuppressants/-modulants?

Immunomodulatory and immunosuppressive therapies can influence the response to vaccination. Previous studies investigated the antibody response after vaccination against tetanus, influenza, pneumococcus, and varicella in rather small cohorts and focused on the humoral immune reaction. Data on the immune response to vaccinations studied so far (no COVID-19 vaccinations) under different DMARDs are listed in [Table 7](#) (Appendix).

It is uncertain whether the results of these studies can be extrapolated to the SARS-CoV-2 vaccines and whether there is a difference between the mRNA and vector vaccines. It can also not be assumed that assessment of the humoral immune response alone is sufficient to assess the efficacy of the SARS-CoV-2 vaccination.

In the meantime, some studies on vaccination against SARS-CoV-2 have also been able to show that antibody formation depends on the existing immunosuppres-

sion. In the first study worldwide using a small cohort of IRD patients, mainly under biologic therapy, the Kiel working group led by B. Hoyer found an immune response in all of them after mRNA vaccination, although the antibody titres against SARS-CoV-2 were (slightly) reduced compared to healthy controls [61]. Colleagues from Erlangen were then able to show that a certain reduction in the humoral vaccination response can be observed, especially with methotrexate and also with JAK inhibitors [62]. Complete nonresponders were only observed in the Erlangen cohort, the explanation for this is still pending. In both the Kiel and Erlangen studies, it should be noted that the patient cohort was significantly older than the healthy controls and that in the Kiel cohort a large proportion of the differences were no longer statistically significant in an age-matched analysis, which could also be the case for the Erlangen data. This would be supported by the fact that in this study a reduction in the humoral vaccination response was also found in patients without immunosuppression, which would argue for immune senescence as an explanation. The reduction of antibody titres in the Kiel cohort was independent of whether the basic therapy was paused around the vaccinations or not—however, in this cohort, there were neither patients under JAK inhibitors nor under methotrexate.

For RTX, it could be shown in a study with 5 patients [73] and another with 30 patients [74] that antibody formation after COVID-19 vaccination is significantly suppressed depending on the time elapsed since the last administration of RTX. However, an antigen-specific T-cell response remained mostly present. In the second study, the detection of vaccine antibodies was also dependent on the presence of peripheral B cells in the blood. In another study, positive SARS-CoV-2 antibody titres were detected in a total of 94% of 404 IRD patients vaccinated with mRNA vaccines. While 100% of patients under TNF inhibitors showed a humoral vaccination response, this was only the case in 26% of patients under rituximab, albeit with an unclear time interval between the last administration and vaccination, and in 73% under mycophenolate [75].

Table 4 Expert consensus on possible adjustments of antirheumatic therapies in the context of vaccinations against COVID-19		
Medication	Possible adjustments in the context of vaccinations	LoA (± SD)
<i>Pauses or postponements are not generally recommended. In the case of a sustained remission, the following therapy adjustments can be considered in consultation with the rheumatologist in the context of vaccination</i>		
Prednisolone ≤ 10 mg per day	No change	9.74 (± 0.55)
Prednisolone > 10 mg per day	If possible, reduction to lower doses (≤ 10 mg daily)	8.63 (± 2.25)
Hydroxychloroquine	No change	10 (± 0)
Methotrexate	Pause for 1(–2) weeks after each vaccination	7.79 (± 2.76)
Sulfasalazine, leflunomide, azathioprine, calcineurine inhibitors	No change	9.63 (± 0.67)
Belimumab	No change	8.84 (± 1.63)
TNF- α , IL-6-R- α , IL-1- α , IL-17- α , IL-12/23- α , IL-23- α	No change	9.95 (± 0.22)
JAK inhibitors	Pause for 1–2 days before to 1 week after each vaccination	7.74 (± 2.63)
Abatacept (sc)	Pause for 1 week before and 1 week after each vaccination	8.47 (± 1.67)
Abatacept (iv)	Vaccination in the interval between two infusions; if possible 4 weeks after an infusion with delay of the next infusion by 1 week	8.53 (± 1.63)
Rituximab	Consider alternative therapy and carry out vaccination	9.42 (± 1.27)
	Postponement of the first or next RTX cycle to 2–4 weeks after completion of the vaccination series	8.68 (± 1.92)
	If possible, vaccination at the earliest 4–6 months after the last RTX administration	9.53 (± 0.75)
	For patients at risk, earlier vaccination if necessary	9.11 (± 1.17)
Mycophenolate	Pause for 1 week after each vaccination	7.53 (± 2.11)
NSAIDs and paracetamol	Pause for 6–24 h (according to half-life of NSAID) before and 6 h after every vaccination	7.68 (± 2.77)

At the end of May 2021, a retrospective study from two cohorts located in New York and Erlangen was published, in which a reduced humoral and cellular response after vaccination with the Pfizer/BioNTech vaccine under methotrexate was reported in some of the vaccinated patients [76]. It remains questionable whether isolated subgroup analyses by age (comparison of those under 55 years of age, as methotrexate patients were 10 years older on average) and by COVID-19 already experienced (8% in the methotrexate group versus 15% in controls and 19% in patients on other therapies) were still statistically adequate. In addition, vaccination response

was tested quite shortly after the second vaccination (8–14 days, assuming a vaccination interval of 21 days). So it cannot be ruled out that vaccination response is only delayed. The authors themselves also point out that it is not yet clear what level of immune response is sufficient for a vaccine to be effective. The arbitrarily defined cut-offs do not allow any conclusion as to whether the failure to achieve the desired humoral immune response is also associated with a higher risk of infection. The question of whether ongoing methotrexate therapy in fact weakens the immune response after SARS-CoV-2 vaccination in a relevant way cannot be answered with

certainty based on the available data, and it is even less clear whether this reduces vaccine protection.

8.12 Should immunosuppressive/immunomodulatory therapy be reduced or paused because of vaccination?

Data on temporary pauses of DMARDs at the time of the SARS-CoV-2 vaccination is limited and refers predominantly to patients with inflammatory joint diseases. Controversy surrounds the study data on methotrexate, which showed an improved humoral immune response with a 2-week break after influenza vaccination. Other data show an increased rate of relapses of IRD with methotrexate paused > 2 weeks, without any further improvement in the immune response. For tofacitinib, it was shown that a 1-week therapy break before and after pneumococcal vaccination did not result in a better immune response. Comparable data on other DMARDs are not available.

For basic considerations of the effectiveness of vaccination, immunosuppression should be as low as possible at the time of vaccination, but not only with regard to vaccinations against SARS-CoV-2, the risk of reactivation of IRD after a longer pause or discontinuation of immunomodulatory/immunosuppressive therapy is estimated to be higher than the benefit of an even potential improvement of the vaccination response. Therefore, we do not recommend regularly changing an existing immunomodulatory/immunosuppressive therapy because of the vaccination. An exception is the administration of long-acting B-cell depleting substances (RTX). In this case, consideration should be given to postponing or switching to alternative therapies, taking into account the risk of reactivation of the underlying disease on the one hand and the improvement of a potential vaccine response on the other (see [Table 4](#)).

Good disease control is also a priority in the context of vaccination against COVID-19. Patients should be informed and involved in the decision-making process if there is even a temporary change in therapy. In order to optimise the vaccination response and in consultation

with the treating rheumatologist, a pause of methotrexate, mycophenolate, JAK inhibitors, and abatacept around the COVID-19 vaccination can be considered in the case of well-controlled IRD (■ [Table 4](#)).

8.13 Vaccination sequence

No specific restrictions or changes are seen compared to the time sequences of vaccinations given by the STIKO for patients with IRD. Depending on the urgency of an immunosuppressive therapy that impairs the vaccination response (i.e. especially in the case of planned administration of RTX), the shortest possible intervals between the first and second vaccination should be aimed for, as far as the approval permits, or a single vaccination with a vector vaccine (Johnson & Johnson) (see section 8.9). When administering RTX, a time window of 4 (in urgent cases at least 2) weeks after completion of the COVID-19 vaccination should be observed.

8.14 Can the success of a vaccination against COVID-19 be checked by titre testing?

Under any immunosuppression, the vaccination response may be reduced (see section 8.11). The antibody response after vaccination against COVID-19 can be checked by lab testing of antibody titre. However, routine determination of antibodies against SARS-CoV-2 is not recommended [77], as it cannot yet be assessed whether these are suitable as surrogate markers for existing immunity, even though there is increasing evidence that neutralising antibodies are predictive of protection against symptomatic infection [78]. With the currently available tests, it is not yet possible to give a precise statement at which antibody level there is actual protection against the disease. Even in the case of a complete absence of antibodies, a cellular immune response against the spike protein could exist and thus a vaccination protection could be present. This is not detected by antibody tests. In the case of low or negative antibodies, it should therefore not be concluded that the vaccination response against COVID-19 has completely

failed and that patients are not protected against infection.

Even with a history of infection, routine titre control is not recommended prior to vaccination, as vaccination is recommended regardless of antibody findings.

However, it should be noted that the interpretation of humoral and cellular immunity is a dynamic process and a new assessment of the value of these tests, especially with regard to the evaluation of the need for a booster vaccination in immune suppressed persons with an insufficient vaccination response, may occur quickly. With regard to booster vaccination, a precise assessment will only be possible when criteria for an effective protective effect are defined and controlled studies on booster vaccination (including timing, quantity, active ingredient) are available.

8.15 Other vaccinations

Independent of the considerations on SARS-CoV-2, other vaccinations should be given according to the recommendations of the STIKO. Data on interactions between these and other known vaccines on the one hand and the SARS-CoV-2 vaccines on the other are not available. A minimum interval of 14 days before the start and after the end of the vaccination series against SARS-CoV-2 should be reserved for other vaccinations (with the exception of emergency vaccinations).

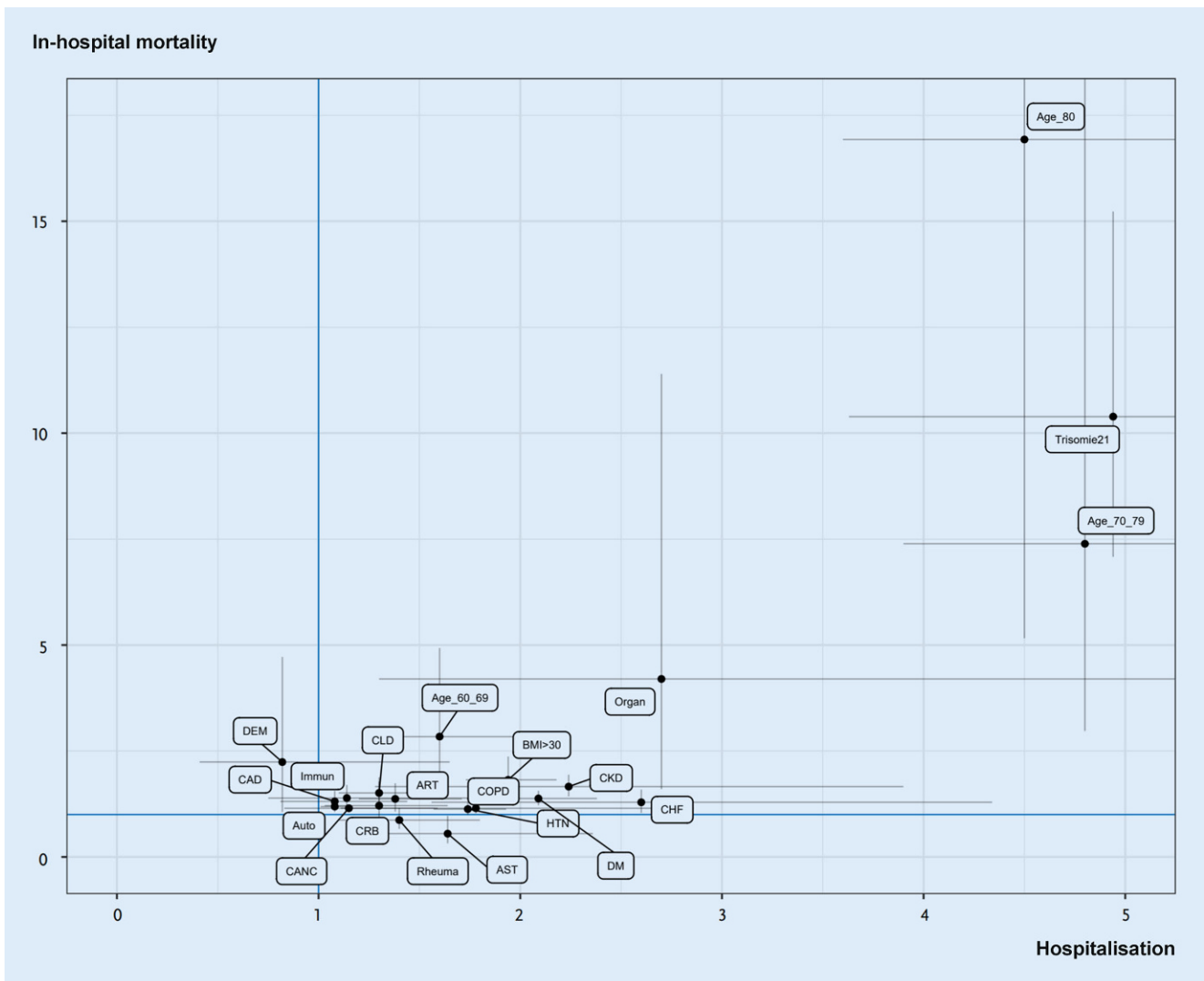


Fig. 1 ▲ Cluster-analysis—risk of different pre-existing conditions and age on hospitalisation and mortality in the context of COVID-19 (from [8]). *ART* arrhythmia or atrial fibrillation; *CHF* congestive heart failure; *CAD* coronary artery disease; *HTN* hypertension; *DM* diabetes; *BMI > 30* obesity & overweight; *CANC* cancer; *AST* asthma; *COPD* chronic obstructive pulmonary disease; *CKD* chronic kidney disease; *CLD* chronic liver disease; *CRB* cerebrovascular or stroke; *DEM* dementia; *Auto* autoimmune condition; *Immun* immunodeficiency or immunosuppressed state; *Rheuma* (inflammatory) rheumatic disease; *Organ* organ transplant history

Table 5 Various studies on the odds ratio (OR) of IRDs for a severe course, hospitalisation or death in association with COVID-19

Reference	Diagnosis	Number of patients/total IR- population	End point	OR (CI 95%)
<i>Bachiller-Corral J, J Rheumatol 2020 [28] (retrospective monocenter cohort study)</i>	SLE	254/4592	Hospitalisation	3.38 (1.28–8.95)
	Sjögren's syndrome	175/4592		4.9 (1.86–12.94)
	PMR	474/4592		2.71 (1.23–6.02)
	Vasculitis (vs. general population)	165/4592		3.9 (1.27–11.99)
<i>Cordtz R, Rheumatology 2020 [29] (Denmark, national cohort study)</i>	RA	29,440 (davon 69 hospitalisiert)/58,052	Hospitalisation	1.46 (1.15–1.86) ^b
	Vasculitis (vs. general population)	4072 (davon 8 hospitalisiert)/58,052 4.5 Million		1.82 (0.91–3.64) ^b
<i>FAI²R, Ann Rheum Dis 2021 [13] (France, registry data)</i>	Vasculitis	65/694	Serious course	2.25 (1.13–4.41) ^a
			Death	2.09 (0.93–4.56) ^a
	Autoinflammatory syndromes (vs. "matched cohort" of non-IRD COVID patients)	12/694	Serious course	7.88 (1.39–37.05) ^a
			Death	2.56 (1.15–5.95) ^a
<i>Freitez-Nunez, Ann Rheum Dis 2020 [18] (monocentric cohort study)</i>	Systemic autoimmune diseases (vs. RA)	123 (50 thereof with RA)	Hospitalisation	3.55 (1.30–9.67)
<i>Pablos J, Ann Rheum Dis 2020 [12] (multicentric cohort study)</i>	CTD ^c (vs. matched non-IRD cohort)	228 IRD-patients (40% with CTD)	Serious course	1.82 (1.00–3.30)

^aadjusted OR
^bhazard ratio
^cCTD in this study with the following diagnoses: polymyalgia rheumatica, systemic lupus erythematosus, Sjögren's syndrome, systemic sclerosis, primary antiphospholipid-syndrome, giant-cell arteriitis, myositis, other vasculitides

Table 6 Common COVID-19 symptoms in patients with inflammatory rheumatic diseases in Germany. Data from the COVID-19 rheumatism registry [6]—with 2729 patients enrolled—(as of 23 May 2021)

Symptom	% (multiple answers)
Cough	55
Fatigue	52
Fever	49
Myalgia	36
Loss of taste	34
Headache	32
Loss of smelling	32
Dyspnoea	25
Common cold	22
Loss of appetite	22
Diarhoea	13
Vertigo	12
Expectoration	10

Table 7 Studies on vaccination response under prednisone and DMARDs (no COVID-19 vaccinations)

Compound	Data on vaccination response
<i>Prednisone [79–81]</i>	> 10 mg Prednisone (dose-dependent) limited humoral response
<i>csDMARDs</i>	
Methotrexate [82–85]	Decreased humoral response (influenza, pneumococcus)
Mycophenolate [75]	Decreased humoral response
Other csDMARDs [86–89]	Limited, but acceptable humoral response
<i>bDMARDs</i>	
TNF inhibitors [81, 86, 90–92]	Limited, but acceptable humoral response (influenza)
IL-6-R inhibitors [93–95]	Unimpaired humoral response
Abatacept [95–97]	Inconsistent data
Rituximab [82, 98–100]	Significantly impaired humoral response (pneumococcus, influenza)
<i>tsDMARDs</i>	
JAK inhibitors [101–103]	Unimpaired humoral/cellular response (pneumococcus) Impaired humoral response (tetanus)

Research agenda

- Are patients with certain inflammatory rheumatic diseases (IRD) or organ involvement at increased risk of COVID-19 or severe progression?
- Are certain antirheumatic therapies/therapeutic principles associated with an increased risk of COVID-19 or severe progression?
- Are glucocorticoids also associated with an increased risk of COVID-19 or a severe course, independent of disease activity?
- To what extent do other vaccinations (e.g. against influenza, pneumococcus) have a positive effect on the course of COVID-19?
- Is pausing/discontinuing DMARD therapy before/after COVID-19 vaccination associated with an improved immune response? How long should the pause be for each therapy?
- What humoral or cellular immunity tests are useful to assess adequate protection against infection after infection or vaccination?
- What is the significance of SARS-CoV-2 antibody determinations with regard to protection against newly emerging virus variants?
- When and at what frequency are booster vaccinations useful?
- Is it useful to determine peripheral B cells before vaccination?
- Is there a preference for certain vaccines in the context of rheumatic diseases?
- How protective are vaccinations in terms of frequency and severity of COVID-19 in IRD?
- Is the influence of costimulation blockade particularly relevant in the primary response (first vaccination)?

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Declarations

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Ethical standards. For this article no studies with human participants or animals were performed by any of the authors.

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