Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

The COVID-19 pandemic and ANCA-associated vasculitis – reports from the EUVAS meeting and EUVAS education forum

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A B S T R A C T

The Coronavirus Disease 2019 (COVID-19) pandemic influenced the management of patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. A paucity of data exists on outcome of patients with vasculitis following COVID-19, but mortality is higher than in the general population and comparable to patients undergoing haemodialysis or kidney transplant recipients (reported mortality rates of 20–25%). Delays in diagnosis have been reported, which are associated with sequelae such as dialysis-dependency. Management of ANCA-associated vasculitis has not changed with the aim to suppress disease activity and reduce burden of disease. The use of rituximab, an important and widely used agent, is associated with a more severe hospital course of COVID-19 and absence of antibodies following severe acute respiratory syndrome (SARS)-CoV-2 infections, which prone patients to re-infection. Reports on vaccine antibody response are scarce at the moment, but preliminary findings point towards an impaired immune response, especially when patients receive rituximab as part of their treatment. Seropositivity was reported in less than 20% of patients when rituximab was administered within the prior six months, and the antibody response correlated with $CD19^+$ B-cell repopulation. A delay in maintenance doses, if disease activity allows, has been suggested using a $CD19^+$ B-cell guided strategy. Other immunosuppressive measures, which are used in ANCA-associated vasculitis, also impair humoral and cellular vaccine responses. Regular measurements of vaccine response or a healthcare-policy time-based strategy are indicated to provide additional doses ("booster") of COVID-19 vaccines. This review summarizes a recent educational forum and a recent virtual meeting of the European Vasculitis Society (EUVAS) focusing on COVID-19.

1. Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic changed interactions among scientists, clinicians and healthcare professionals globally. The EUVAS meeting was scheduled in Salzburg on November 2nd 2020 but had to be conducted as a virtual meeting. One of the sessions of the meeting was dedicated to COVID-19, with two presentations focusing on COVID-19-related outcomes for patients with vasculitis. A project proposal aimed to shed light on management of de novo or relapsing anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis during the first wave of the pandemic and if specialist centres modified their induction treatment regimens.

As European Vasculitis Society courses could not be held in 2020 and 2021, an educational programme was initiated virtually to discuss topics relevant to the field. A recent educational forum focused on specific considerations of patients with ANCA-associated vasculitis and COVID-19 vaccination. Important questions about COVID-19 and ANCA-associated vasculitis, such as routine management, diagnosis and management of SARS-CoV-2 infections, as well as important questions about management during the vaccination process need to be answered. Selected questions with high priority are summarized in Boxes 1 and 2.

This review article aims to summarize similarities in pathogenesis of COVID-19 and ANCA-associated vasculitis; our understanding of the pandemic's impact on management of vasculitis patients, their specific outcomes after severe acute respiratory syndrome (SARS)-CoV-2 infections; the potential impact of long COVID, and also discusses recent

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literature/reports about COVID-19 vaccination relevant to ANCA-associated vasculitis. This is of particular relevance as most countries are lifting COVID-19 related restrictions despite facing another surge of infections due to variants of concerns and many patients with ANCA-associated vasculitis are left with minimal/no protection to contract COVID-19 and a potential severe disease outcome. Importantly, multinational efforts which have always be a cornerstone of EUVAS research are urgently needed to provide a better guidance for clinicians and our patients.

2. COVID-19 and ANCA-associated vasculitis

2.1. Shared characteristics of COVID-19 and ANCA-associated vasculitis

Similar pathways are involved mechanisms of disease involving COVID-19 and ANCA-associated vasculitis. For instance, neutrophil extracellular traps (NETs) are induced in both entities. High levels of NETs were found in SARS-CoV-2 infections with severe organ damage, and high mortality rates [1], similar to ANCA-associated vasculitis, in which complement activation and endothelial dysfunction are induced by NETs [2]. The alternative complement pathway plays a central role in ANCA-associated vasculitis [3], and inhibition of the C5aR1 receptor is a promising tool in the disease management [4]. Similarly, the C5a-C5aR1 receptor axis is prominently involved in COVID-19, and C5aR1 inhibition prevented acute lung injury in a C5aR1 knock-in model [5]. A phase 2 trial investigating the monoclonal antibody IFX-1 that inhibits C5a proved to be safe and demonstrated efficacy in patients with COVID-19 [6], with a larger phase 3 trial currently ongoing. It seems that a delicate interplay between NETs and complement is involved in the prothrombotic affinity of both diseases [7–10]. Venous thromboembolic event (VTE) rate is high in both entities, with approximately 30% of severe COVID-19 cases with confirmed VTE [11,12] and over 10% reported in several investigations of patients with ANCA-associated vasculitis [13]. Comparing SARS-CoV-2 with influenza-affected lungs, it was found that neutrophil recruitment exerted by a $HLADR^{low}$ $CD9^{low}$ monocyte population was more prominent in COVID-19, releasing neutrophil cytokines in the lungs and leading to the expansion of neutrophil subsets, eventually inducing thrombosis in severe disease. These alterations were not restricted to lung specimens, but also observed in the kidney and heart of patients with severe COVID-19 [14]. Post-mortem analyses of lungs indicated patchy mononuclear-cell vasculitis involving the intima of small−/medium-sized pulmonary arteries in four of eleven cases analysed. The immune infiltrate was dominated by a myeloid-related protein 8 $(MRP8)^{+}$-rich infiltrate, accompanied by $CD4^{+}$ and $CD8^{+}$ T cells and macrophages [15].

Cases of de novo ANCA-associated vasculitis are reported in literature [16–18]. There is uncertainty about co-incidence of such cases or true association, but it seems that SARS-CoV-2 infections induce molecular mimicry [19,20] and the production of autoantibodies [21,22], as a consequence of stimulation of the innate and adaptive immune system. Cytokine storm might in part be responsible for this inadequate immune response [23]. Other severe autoimmune disorders have been reported during or following SARS-CoV-2 infections [24–28].

2.2. Outcome of patients with ANCA-associated vasculitis affected by COVID-19

One year into the pandemic, there remains paucity of data about mortality and specific risk factors for patients with ANCA-associated vasculitis contracting COVID-19. Based on analysis of rare

Box 1
Several important research questions are summarized, which are key to understand the impact of COVID-19 on mortality of patients with ANCA-associated vasculitis, diagnosis of new cases and relapses, risk factors for worse outcomes, persistent symptoms after SARS-CoV-2 infections as well as impact on induction and maintenance treatment.

Focus	Research questions	Related issues
Mortality	What was the mortality rate of patients with ANCA-associated vasculitis during the pandemic in comparison to the years before (at a population-based level)? How does COVID-19 related mortality change over time?	Reporting bias towards more severe cases may likely overestimate the mortality rate. Better prognosis due to optimised COVID-19 management strategies such as dexamethasone, understanding the effect of tocilizumab, casirivimab/imdevimab, and others.
Diagnosis/ Diagnostic delay	How can referral strategies be maintained or telemedicine options improved to reduce the burden of damage attributable to a diagnostic delay?	
Risk factors	What are specific risk factors for worse disease outcome?	Consider age groups, chronic kidney disease, time elapsed from initial diagnosis/relapse to COVID-19, specific treatment approaches.
Long COVID	What are sequelae of SARS-CoV-2 infections? What is the impact on pre-existing damage/reduced quality of life of patients with ANCA-associated vasculitis?	
Induction treatment	What is the optimal approach to a patient with active ANCA-associated vasculitis and concomitant COVID-19?	Consideration on optimal induction treatment in a pandemic situation (e.g less rituximab)?
Maintenance treatment	What is the optimal approach to a patient with ANCA-associated vasculitis in remission? What is the optimal approach to achieve a vaccine response (humoral/cellular immunity) “preparedness”?	Consider to reduce hospital visits. Consider measures to reduce the risk of disease relapse and intensification of immunosuppressive therapy (e.g., implementation of a hotline/e-mail address with daily response options). Evaluate safety to discontinue / postpone maintenance therapy (e.g. postpone rituximab by 3 months or guide according to CD19+ B-cells).

autoimmune rheumatic diseases, a study from the UK found a 1.44 times greater standardized mortality rate during the first wave of the pandemic (March and April 2020) when compared to the same months of the previous 5 years [29]. A recent analysis of the COVID-19 Global Rheumatology Alliance registry assessed the COVID-19-related mortality of 3729 patients with an overall fatality rate of 10.5%. Of 326 patients included with a diagnosis of vasculitis (not restricted to ANCA-associated vasculitis), 68 (17.4%) deceased. Among patients with either vasculitis or connective tissue diseases, older age groups, chronic lung or kidney disease, higher disease activity scores, any immunosuppressants, treatment with rituximab, and current glucocorticoid exposure (even low doses between 1 and 10 mg/day) emerged as independent risk factors associated with COVID-19-related death [30]. While these findings point towards an increased risk of mortality in these vulnerable patient groups, no large population-based study focused on ANCA-associated vasculitis as a single entity. Two independent projects, one using the UK and Ireland Vasculitis Society (UKIVAS) and the Irish Rare Kidney Disease (RKD) registries [31] and one using a population-based cohort in Sweden (not yet published), were presented at the European Vasculitis Society meeting and aim to close this knowledge gap.

Rutherford et al. included 65 cases of patients with systemic vasculitis who developed COVID-19, of whom 55 had a diagnosis of ANCA-associated vasculitis. Active disease was present in thirty-two patients (49%), and background glucocorticoids were prescribed in 69% of patients, with a dose equivalent of 5 mg prednisone or less in 29%, and more than 5 mg in the remaining 40%. Recent administration of rituximab and/or cyclophosphamide was recorded in 34% and 15% of patients. A majority of patients were hospitalized (91%), while 11% required intensive care unit (ICU) treatment and 28% died. Further analyses revealed that a severe COVID-19 outcome was associated with the presence of comorbid respiratory diseases and the prescription of glucocorticoids [31]. The use of glucocorticoids at a dose higher than 10 mg daily prednisone/prednisolone (or equivalent) was not only associated with a higher probability of contracting COVID-19 but was also related to severe disease and COVID-19-related death in inflammatory rheumatic diseases [32]. These findings seem paradoxical to findings from the RECOVERY trial, as dexamethasone at a daily dose of 6 mg resulted in lower 28-day mortality in patients requiring oxygen or invasive mechanical ventilation [33]. Factors leading to this discrepancy remain obscure, but glucocorticoids may impact initial viral clearance and the addition of dexamethasone may only be beneficial in COVID-19 cases with signs of hyperinflammation.

In patients with ANCA-associated vasculitis, similar risk factors as in the general population seem to predict severe outcomes of COVID-19, including age, co-morbidities and male sex. Furthermore, even patients with severe COVID-19 may fail to mount an antibody response to SARS-CoV-2, especially when recently receiving rituximab infusions [34]. Such patients may also be at risk of re-infection with COVID-19, as was shown by a case receiving rituximab induction therapy and presented with two symptomatic SARS-CoV-2 infections within six months [35]. In addition to a frequently negative antibody test result following infection, patients tend to have a longer period of symptoms and an impaired ability to clear the virus as shown by a longer presence of positive PCR tests [36]. A larger single-centre study included twenty cases with COVID-19 and found that severe COVID-19 outcomes, which were observed in eight patients, were associated with active ANCA-associated vasculitis [37]. Of importance, most patients with ANCA-associated vasculitis survive COVID-19, even in the absence of antibodies to SARS-CoV-2. This points towards the importance of cellular immune responses.

Box 2
Several points are critical to answer to understand the efficacy of COVID-19 vaccines in patients with ANCA-associated vasculitis, especially the strength of humoral response to protect from severe disease and the impact of cellular immunity in those without detectable antibodies.

Focus	Research-related issues	Considerations
Measurement of humoral and cellular immunity	Measurement of antibody levels at various time-points. How do various agents impair vaccine response?	Measure antibodies 2–4 weeks after completion of the vaccination, measure cellular response (if feasible) at the same time-point. In positive patients, measure antibodies during routine clinical follow-up (first assessment after 3 months or during routine controls?) Attributes of different immunosuppressive measures: rituximab, cyclophosphamide, azathioprine, mycophenolate mofetil, high-doses of steroids.
Efficacy outcome	Assessment of efficacy of different vaccine platforms to prevent mild/moderate COVID-19 and especially severe/life-threatening SARS-CoV-2 infections.	Is a cellular immune response sufficient to prevent severe disease (especially in rituximab-treated patients)? Consider booster doses early after vaccination.
Vaccination after SARS-CoV-2 infection	What is the risk of re-infection of patients following COVID-19? When is the ideal timepoint to vaccinate patients?	Define the vaccine response in patients with pre-existing antibodies; is one dose of the respective vaccine sufficient to mount an adequate immune response or do patients need a second dose.
Use of different vaccines (if unresponsive)	What strategy should we use in patients who fail to mount an adequate immune response?	Administration of additional doses of the same or different vaccines (“heterologous vaccination strategy”) or different routes of administration (e.g. a respiratory booster dose, if approved) may be considered.
Safety	Systematic assessment of systemic/local reactions. Impact of COVID-19 vaccines on relapse risk/risk to develop de novo disease.	

2.3. Treatment strategies of ANCA-associated vasculitis during the pandemic

Another international multicentre study aimed to investigate how treatment approaches to manage active ANCA-associated vasculitis (either de novo or relapsing) have changed during the first months of the pandemic (January to July 2020) and patients will be followed for at least twelve months from inclusion. Overall, 191 patients from the United States ($n = 44$), United Kingdom ($n = 83$) and Europe ($n = 64$) were recruited. Preliminary results indicated that sixteen patients contracted COVID-19 and four of them died. Overall, sixteen deaths (8.4%) including four COVID-19-related were recorded during short-term follow-up of six months (other reasons of death remain unclear). Importantly, treatment regimens did not dramatically change during the first wave of the pandemic, and in brief 84 patients received rituximab, 49 received cyclophosphamide and another 49 received a combination of rituximab and cyclophosphamide. Pulsed steroids followed by oral administration were used in most of the patients. Based on the treatment approaches used during the initial phase of the pandemic, experts aimed to not "undertreat", that means that vasculitis should be controlled according to currently available standards. Specific treatment recommendations for patients with ANCA-associated vasculitis were issued during the initial phase of the pandemic, while others focused on immune-mediated kidney diseases or those receiving immunosuppression (including kidney transplant recipients) [38–40].

2.4. Management of COVID-19 in vasculitis patients

The reported cases of newly diagnosed ANCA-associated vasculitis with concomitant COVID-19 have been treated on a case-by-case decision. Fourteen patients on maintenance therapy (11/14 received rituximab) were reported in a recent publication. All but one of the reported patients ($n = 18$; 4 patients with a new diagnosis) of this case series survived. COVID-19 treatment was used at investigator's discretion, and included hydroxychloroquine ($n = 7$), antibiotic measures such as azithromycin ($n = 4$), and ritonavir/lopinavir ($n = 4$) in earlier cases, while tocilizumab ($n = 2$), convalescent plasma ($n = 2$), remdesivir ($n = 4$), and dexamethasone (2) were used in more recent cases [41]. Notably, most of these agents have been tested in large randomised controlled trials and proven to be ineffective in the meantime, and therefore, would not be used at the time of publication of this report any more.

2.5. Impact of the pandemic on patients living with vasculitis and the time to initial diagnosis

A Vasculitis Patient-Powered Research Network survey found a high level of concern about COVID-19 in patients with vasculitis. The use of immunosuppression, older age, female sex and comorbid pulmonary disease influenced the level of concern. These concerns had a direct impact on avoidance of seeing a doctor and undertaking laboratory and other tests. Higher density of immunosuppression (including prednisone use of more than 10 mg a day) was associated with a greater likelihood of avoiding tests or visits. An alarming number of patients (10.5%) stopped their immunosuppression, without consultation with their managing physician. Moreover, a temporary halt of rituximab (7.5%) or avoidance (13.3%) to receive further rituximab was reported. Information on outcome (i.e. relapses) was not part of the survey [42]. The first wave of the pandemic had a significant impact on patient care. A survey conducted at two sites, one in the US and one in the UK, found that while there were no in-person visits, while 69% had video visits ($n = 142$), 13% of visits were rescheduled ($n = 26$), and 11% had no change in health care ($n = 23$). Maintenance therapy with rituximab was postponed in 21 patients (denominator unclear as applications not stated), and 12 patients had a disease relapse during this period of observation. Among these patients, one missed a scheduled rituximab infusion, while one with a postponed dose of rituximab relapsed [43].

These concerns about attending hospital appointments might also lead to delays in making an initial diagnosis of vasculitis or confirming a disease relapse. Diagnostic delay has been reported from an Italian centre in an observational study, with a high proportion of patients presenting with dialysis-dependent kidney failure (seven of nine patients) [44]. Another single-centre observational study found an increase in newly diagnosed ANCA-associated vasculitis after the first lockdown (eleven patients with a new diagnosis from May to August 2020, 3-fold increased incidence of new cases in 2020 compared to 2015–2019). Referral patterns and damage attributable to vasculitis were comparable to the years before the pandemic [34,45].

2.6. Long COVID: a big deal in patients with ANCA-associated vasculitis?

Post-acute sequelae of SARS-CoV-2 infection, or long COVID, are increasingly recognised in the general population. Results of a standardized interview of 410 patients with COVID-19 during the first wave of the pandemic revealed that 7 to 9 months after infection, 39.0% still reported residual symptoms. These included fatigue (20.7%), anosmia and/or ageusia (16.8%), dyspnoea (11.7%), headache (10.0%), cough (3.7%), and digestive symptoms (2.2%) [46]. A similar frequency of persistent symptoms was found among 177 participants of a survey six months following SARS-CoV-2 infection. Notably, frequencies were comparable between outpatients (49 of 150, 32.7%) and patients who required hospitalisation (5 of 16, 31.3%) [47]. This implies that patients with milder COVID-19 symptoms are equally affected by long-term sequelae which impair quality of life. Information on long-term symptoms after SARS-CoV-2 infections is not available for patients with ANCA-associated vasculitis, but patients commonly report fatigue symptoms and it is a major contributor to impaired quality of life [48]. Moreover, there might be difficulties to distinguish fatigue due to COVID-19 and/or vasculitis. Hyposmia/anosmia is one of the leading long COVID symptoms and is also reported in patients with granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [49,50]. Again, an interplay between COVID-19 and ANCA-associated vasculitis may aggravate the symptoms.

3. ANCA-associated vasculitis and COVID-19 vaccination

3.1. What is known from other vaccines?

There has been a general concern about impaired vaccine responses in individuals with primary or secondary immunodeficiencies and their ability to mount an adequate response towards COVID-19 vaccines in particular. The pre-COVID-19 time left us with little evidence and information about vaccine response of patients with ANCA-associated vasculitis. A small randomised controlled trial found that the seroconversion rate towards influenza A H1N1, A H3N2 and B. malay of patients was lower in comparison to healthy controls, and lower antibody titres, ranging from 31% to 62%. No increase in ANCA titres was observed after vaccination, and no relapse was recorded among 24 patients with ANCA-associated vasculitis [51]. Another investigation with a large proportion of patients in remission and off immunosuppression (47%) found a good efficacy and safety, with a reduced response to influenza A H1N1 but a comparable response to A H3N2 and B. Vaccination did again not influence ANCA titres [52]. The cellular immune response, measured in 24 patients (of whom 13 were off immunosuppression), showed a comparable response as healthy controls [53]. These reports included patients in the "pre-rituximab" era and no information about vaccine response following B-cell depletion was reported. Investigations in cohorts including different immune-mediated diseases found that antibody response to vaccination is blunted following rituximab [54], and some reported impaired humoral response to glucocorticoids [55].

3.2. "Vaccine readiness": what does that mean?

Patients receiving immunosuppressive drugs have been excluded from most phase III trials investigating COVID-19 vaccines [56]. The level of neutralising antibodies seems to correlate with protection against SARS-CoV-2 infections, and a low level of antibodies (around 3% of the mean convalescent level) is required to have a 50% protection from severe disease [57]. From the experience during the early phase after vaccine rollout, it seems pivotal to mount a humoral vaccine response. A multi-centre survey from France on SARS-CoV-2 infections following two doses of mRNA vaccines, either BNT162b2 or mRNA-1273, indicated that 24 of 25 patients with COVID-19 had undetectable antibodies, and the titre in the remainder was low. The disease course was comparable to patients without prior vaccination [58]. The term "vaccine readiness" was stressed in the past, which is defined as enabling vaccine response in patients receiving immunosuppression. In the context of vasculitis or autoimmunity, this has been particularly discussed in patients receiving rituximab as maintenance therapy, as these patients frequently fail to show an antibody response following vaccination [56,59–63].

3.3. Rituximab and immune response – time to delay vaccination?

In patients on maintenance doses of rituximab and stable remission, a delay in rituximab or a transient switch to other immunosuppressive measures (such as azathioprine) may be warranted. A B-cell driven tailored approach as tested in the MAINRITSAN2 trial confirmed that this strategy is acceptable in terms of relapse risk (7.4% more relapses), but with a reduction of 2 infusions over a follow-up period of 28 months. Nonetheless, such a strategy requires more hospital visits, which is undesirable during a pandemic [64]. Data on humoral response of patients with ANCA-associated vasculitis following COVID-19 vaccination are scarce at the moment. A single-centre study from the US included 48 patients, of whom eighteen (37.5%) presented with a positive antibody test. These patients more likely received mRNA-1273 ($n = 14$), in comparison to BNT162b2 ($n = 4$) or Ad26.COV2·S ($n = 0$). Among the twenty-two patients receiving rituximab within the six months prior to vaccine administration, only three (16.7%) had an antibody response, while none of the fifteen who received rituximab within four months of vaccine administration had a positive antibody test. Fifteen of 19 patients with a reconstitution of $CD19^+$ B-cells had a positive antibody test, and patients with no response to vaccination usually had absence of $CD19^+$ B-cells. A significant predictor of humoral vaccine response was time from last rituximab infusion (431 versus 138 days), while hypogammaglobulinemia had no impact on response. Importantly, two patients presented with COVID-19, of whom one died and one was hospitalized [65]. These results of low vaccine response in rituximab users were also confirmed in a study, focusing on 686 patients (12.7% receiving rituximab) with autoimmune inflammatory rheumatic diseases. Rituximab therapy was most frequent in idiopathic inflammatory myositis and ANCA-associated vasculitis. The lowest humoral vaccine response was reported in the groups comprising these entities. The seropositivity rate was below 20% when rituximab was used within 6 months of vaccine administration, while it increased to about 50% in patients vaccinated one year after rituximab treatment [66] (see Table 1). From these early studies, it becomes obvious that rituximab severely impairs humoral vaccine response and patients might not respond to vaccines beyond one year after administration. In context of vaccine shortage, it might be warranted to hold COVID-19 vaccine and wait until patients start to repopulate CD19+ B-cells or schedule rituximab maintenance at a later time point (i.e. 9 months). Nonetheless, in countries with an excess supply, vaccination might be considered in this high-risk population despite a recent application of rituximab followed by monitoring of antibody response, as the application of COVID-19 vaccines might trigger a cellular immune response. Discussion about continuation of shielding measures (see below) with patients is essential and vaccination of household individuals and other close contacts, so-called ring vaccination, a priority as vaccination reduces the transmission rate in households [67]. Specific considerations to improve vaccine response are discussed below. Another question is the timing of rituximab after COVID-19 vaccination. The American College of Rheumatology (ACR) guidance indicates to administer rituximab no earlier than two weeks after finalizing COVID-19 vaccination [68], but evidence for the best interval is still lacking.

3.4. T-cell response – sufficient to protect from severe COVID-19?

In patients with an absence of a humoral vaccine response, it was speculated that a cellular vaccine response might be sufficient to protect from severe SARS-CoV-2 infections. A paucity of data exists in this context. A study of five patients on rituximab maintenance therapy found no antibody response in 3 out of five patients. Investigation of the

Table 1
COVID-19 vaccine response in patients receiving B-cell depletion with rituximab.

Author	PMID	Vasculitis (*n*, % total cohort)	Detection kit	Vaccine	%, positivity (vasculitis)	Important findings
Seyahi	34109466	7 (6.9%)	Elecsys®	CoronaVac	71.4%	All patients with vasculitis were in the low (<117 U/mL) titre group; all 7 rituximab users were in the low titre group.
Spiera	33975857	17 (19.1%)	Elecsys®, Atellica®	BNT162b2, mRNA-1273	52.9%	20/30 rituximab users without serologic response Median time from last infusion to first vaccination was 98 days in antibody-negative patients, 704.5 days in those with positive serology. The percentage of circulating B-cells was 0% and 4% in antibody non-responders vs. responders.
Furer	34127481 (ref. 66)	26 (3.8%)	Liaison®	BNT162b2	30.8%	The time interval between last administration of rituximab and BNT162b2 administration had a significant impact on immunogenicity.
Connolly CM	34029488	3 (15%)	Elecsys®	BNT162b2, mRNA-1273	0%*	55% of the cohort received rituximab; 50% received mycophenolate mofetil (2 patients with neither rituximab nor mycophenolate mofetil). Median timing of rituximab before dose 1 was 14 weeks.
Connolly CM	Accepted (ref. 65)	48 (100%)	Elecsys®, Liaison®	BNT162b2, mRNA-1273,	37.5%	None of the patients receiving their COVID-19 vaccine within 4 months of rituximab administration had detectable antibodies. 3/22 who received rituximab 6 months before COVID-19 vaccination had antibodies. Median CD19+ B-cell count 4 versus 0 (responders versus non-responders). More patients receiving mRNA-1273 had an antibody response.

* The study by Connolly CM, et al. focused on patients with rheumatic diseases and absence of antibody response following two doses of mRNA vaccines.

cellular immunity by use of two interferon-gamma releasing assays revealed that a response was observed in two of these patients [69]. A recent publication also indicated that CD8+ T-cell response to influenza vaccine is blunted in rituximab' users [70]. This finding is in contrast to a recent investigation, showing that 75% of patients (6/8) receiving rituximab have a cellular immune response to vaccination [71]. Patients on maintenance haemodialysis have a weakened immune response to COVID-19 vaccines in comparison to healthy controls, but presence of antibodies is documented in about 90% [72]. A study in haemodialysis patients found that the cellular immune response and antibodies in saliva samples correlated well with the antibodies measured in plasma samples [73], thus indicating that patients with a weakened or no response might also exhibit impaired cellular response to COVID-19 vaccines. From the limited experience it is still unclear what influence commonly used immunosuppressants have on cellular immunity. Furthermore, the potential protection of asymptomatic or symptomatic SARS-CoV-2 infections in the absence of humoral response needs to be studied in more detail.

3.5. Booster doses in non-responsive patients

In general, policies differ in patients with a history of SARS-CoV-2 infection, and one booster dose of COVID-19 vaccine may be sufficient to have an adequate antibody response. In patients without prior SARS-CoV-2 infection, changes in national guidance of most countries allow for additional administration of booster doses of COVID-19 vaccines. Such a strategy was implemented in France after the first reports of an impaired immune response in transplant recipients. First results of 101 consecutive solid-organ transplant recipients receiving a 3rd dose were reported recently. Forty percent of patients had a humoral response before administration of the 3rd dose of BNT162b2. Among the 59 seronegative patients after the 2nd dose, twenty-six (44%) were seropositive four weeks after the booster dose. Importantly, patients with seropositivity after two doses had a 74-fold increase in their antibody levels [74]. This is of particular importance as virus neutralisation of available vaccines is severely reduced against variants of concern such as B.1351 or B.1617.2 [75]. Antibody levels should be measured as part of the routine in all patients during clinical visits and booster doses scheduled early in those with a severely reduced humoral response or no response to vaccination. No information about "ideal" vaccination strategies is thus far available related to ChAdOx1 or Ad26.COV2·S vaccines and their use in immune-mediated diseases. A small randomised controlled trial assigned patients to an intervention group (administration of a single dose of BNT162b2) or observation group following vaccination with a single dose of ChAdOx1. A robust immune response was reported [76], indicating that a heterologous prime boost strategy might also be successfully used in patients with ANCA-associated vasculitis and no humoral response.

3.6. What about other immunosuppressive measures? Do we expect a lower seropositivity rate?

The ACR guidance on COVID-19 vaccination does not suggest any modifications of vaccine administration when patients receive prednisone or azathioprine (strong level of recommendation for prednisone doses <20 mg a day, moderate if equal or higher than 20 mg a day), while for mycophenolate mofetil and methotrexate a hold of one week following each dose is recommended if disease is in stable remission. Cyclophosphamide (intravenous route) should not be administered within one week after each vaccine dose, if feasible [68]. A study investigating different immunosuppressive measures and impact on humoral vaccine response found that the use of glucocorticoids led to a 10-fold reduction in antibody levels. Other measures, such as antimetabolites, also blunted antibody titres [77]. In light of emergence of variants of concerns with a generally lower response to COVID-19 vaccines, these patients should be monitored closely and booster doses scheduled according to antibody titres.

3.7. ANCA-associated vasculitis relapse or de novo disease after vaccination – co-incidence or true association?

Two cases of de novo ANCA-associated vasculitis following COVID-19 vaccination, both presenting with PR3-ANCA vasculitis, have been reported to date [72]. Both presented with severe disease including acute kidney injury. As vaccines per se are stimulating the immune system, including processes of the innate and the adaptive immune response, it would not be surprising that an excess of autoimmunity is observed after COVID-19 vaccine administration. While an association with de novo disease from these early experiences should not be excluded, further investigations on a population-based level are necessary (reports on incidence of ANCA-associated vasculitis). To date, one report of a disease relapse 2 days after the second dose BNT162b2 has been published [78]. Investigations among patients receiving influenza vaccination did not reveal that these vaccines induce disease relapses [79]. Again, further studies are necessary to estimate the risk of relapse following COVID-19 vaccination. Weighing the risk of a relapse against the benefits of COVID-19 vaccination, there is a clear benefit of vaccine administration as most relapses are diagnosed early and can be managed by intensification of immunosuppression.

3.8. What should we recommend after vaccination?

Although restrictions are lifted for vaccinated people, this is not recommended for vulnerable populations. As we have no answers to essential questions raised in Box 2, we further recommend to follow the guidance to reduce social contacts, meet with individuals who have been tested before the meeting (if feasible), to wear a mask, wash your hands regularly and avoid crowded and poorly ventilated spaces. It is of importance that also co-habitants remain vigilant as asymptomatic infections seem to occur after exposure to variants of concern even in vaccinated people.

4. Conclusion

The COVID-19 pandemic poses challenges in the management of diseases such as vasculitides. In patients with a new diagnosis or relapse of ANCA associated vasculitis, achieving disease control should be prioritized to preserve organ function and life and current standard of care induction therapy regimens should be used. Patients with ANCA-associated vasculitis have a higher likelihood of developing severe COVID-19. Nonetheless, many patients after recent rituximab administration are left without detectable SARS-CoV-2 antibodies after infection [66], which eventually increases the risk of re-infection [35]. Vaccines are considered the "game changer" of the pandemic and are effective in the general population to prevent transmission, severe disease courses and mortality due to COVID-19. The seropositivity of patients with ANCA-associated vasculitis is low, and directly depends on the medication used to control the underlying disease. A recent administration of rituximab impairs vaccine response and a delay of maintenance doses, if disease activity allows, is warranted to mount an adequate humoral response. Confirmation of B-cell reconstitution before vaccination may have a bearing on serological conversion. Other immunosuppressive measures commonly used, which include glucocorticoids, antimetabolites and potentially cyclophosphamide, impair the humoral and cellular immune response following COVID-19 vaccination. It is imperative that authorities consider these factors while designing vaccination schedules and provide recommendations for booster doses in this vulnerable population, especially in light of the emergence of variants of concerns. Assessment of cellular and humoral response in vaccinated patients is paramount to reinforce safe behaviour, adopting ring strategy to vaccinate co-habitants and in providing recommendations for a booster vaccine. Effective and timely treatment of vasculitis

(newly diagnosed or relapsing disease) remains a priority, and there is no consensus whether drug protocols should be changed in the face of the pandemic. The European Vasculitis Society discussed several research projects at their virtual meeting on November 2nd and recently discussed COVID-19 vaccination in vasculitis patients on June 25th as part of their educational forum.

Contributors

AK wrote the first draft of the manuscript. All authors provided critical revision of the manuscript. All authors approved the final draft and had the final decision to submit the manuscript for publication.

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Declaration of Competing Interest

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