Provisional recommendations for SARS-CoV-2 vaccination in patients with cryoglobulinaemic vasculitis

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Received on March 11, 2021; accepted in revised form April 12, 2021.

Clin Exp Rheumatol 2021; 39 (Suppl. 129): S149-S154.

Key words: cryoglobulinaemia, COVID-19, SARS-CoV-2 vaccination, autoimmunity

Competing interests: none declared.

ABSTRACT

People with cryoglobulinaemic vasculitis (CV) have an increased risk of infections, attributed to different causes: impairment of the immune system due to the disease itself, comorbidities, and immunosuppressive therapy. Therefore, these patients may be at high risk for a more severe course of COVID-19, including hospitalisation and death.

Concerns about efficacy, immunogenicity and safety of vaccines, as well as doubts, not yet fully clarified in patients with systemic autoimmune diseases, represent other important factors for a low vaccination rate in people with (CV).

Indeed, providing an expert position on the issues related to SARS-CoV-2 vaccination in patients suffering from CV is of critical relevance in order to help both patients and clinicians who are treating them in making the best choice in each case.

A multidisciplinary task force of the Italian Group for the Study of Cryoglobulinaemia (GISC) was convened, and through a Delphi technique produced provisional recommendations regarding SARS-CoV-2 vaccination in cryoglobulinaemic patients.

Introduction

The severe acute respiratory syndrome (SARS) induced by the SARS-Coronavirus-2 (SARS-CoV-2) as part of the Coronavirus Disease-19 (COVID-19) is of particular concern for people with rheumatic musculoskeletal diseases (RMDs) especially those with systemic autoimmune diseases or those who are immunocompromised.

Cryoglobulinaemic syndrome, also called cryoglobulinaemic vasculitis (CV), as vasculitis is the main clinical feature of the disease, is commonly related with viral infections including hepatitis C and B viruses, or systemic autoimmune diseases (mainly, connective tissue diseases). These patients, have an increased risk of infections, attributed to different cause: impairment of the immune system due to the disease itself, comorbidities, and immunosuppressive therapy, including glucocorticoids and biotechnological agents, such as rituximab (1).

Therefore, people with CV may be at high risk for a more severe course of COVID-19, including hospitalisation and death (2).

As suggested by the European League Against Rheumatisms (EULAR) and other international scientific societies, vaccination is of particular importance for these subjects (3). Nevertheless, EULAR pointed out that patients with rheumatic musculoskeletal diseases (RMDs) generally show a suboptimal uptake of vaccinations, also because of the low awareness of the rheumatologist for the need of vaccination (4, 5). Concerns about efficacy, immunogenicity and safety of vaccines, as well as doubts, not yet fully clarified in patients with systemic autoimmune diseases, represent other important factors for a low vaccination rate in people with RMDs.

Even if there might be some uncertainties that antigenic stimulation by vaccination might trigger a nonspecific response, potentially worsening the underlying disease (6, 7), the benefits of vaccination, preventing or reducing the severity of infection, are expected to far outweigh any risk from the vaccine (8).

In last 12 months, a great effort has been made by private companies, governments and no-profit organisations to develop vaccines against SARS-CoV-2, and many Regulatory Authori-

ties have approved COVID-19 vaccines for human use, with other expected to be licensed in 2021 (9). While many countries have started vaccination programmes on the whole population, deployment can also be hampered by vaccine hesitancy, potentially leading to refusal or delayed acceptance of COVID-19 vaccines. Hesitancy is prevalent in low-income and high-income countries alike, with sceptics found in all socioeconomic, religious, and ethnic groups (10).

Therefore, providing an expert position on the issues related to SARS-CoV-2 vaccination in patients suffering from CV is of critical relevance in order to help both patients and clinicians who are treating them in making the best choice in each case.

Methods

A multidisciplinary task force of the Italian Group for the Study of Cryoglobulinaemia (GISC) was convened. Clinical questions were collected, and an evidence report was rapidly generated and shared. Questions and drafted statements were reviewed and assessed using a modified Delphi process. This included asynchronous voting by e-mail.

For approval, median votes were required to meet predefined levels of agreement (median values of ≥70%, >40%, <40%, defined as agreement, uncertainty, or disagreement, respectively). A second round of consultation was carried out for the development of the statements, that were approved if they received a vote rating of ≥70%.

Statements

Patients with cryoglobulinaemic vasculitis (CV) can be defined as fragile and a potential high risk of unfavourable outcome of SARS-CoV-2 infection and should be included among subjects to be vaccinated with priority, preferably using mRNA vaccines. Caution should be used in patients with severe, life-threatening CV. The risk of CV reactivation driven by vaccination can be supposed less relevant than the risks associated with SARS-CoV-2 infection.

Until now, there are no known concerns for SARS-CoV-2 infection vaccination in patients affected by CV. Therefore, available vaccines should be as safe as other vaccinations. Frequency of vaccine-induced autoimmunity is low and available data suggest that the risk-to-benefit ratio is still overwhelmingly in favour of vaccination (9, 11).

Patients affected by another systemic small-vessel vasculitis, namely granulomatosis with polyangiitis (GPA), develop similar humoural responses following influenza-vaccination compared to healthy controls (12). Use of immunosuppressive drugs did not affect the humoural response, and no difference in disease-flare occurrence was found in patients with GPA receiving influenza-vaccination compared to GPA patients that did not receive influenza-vaccination in two prospective studies and one large retrospective study (13, 14).

Among a cohort of unvaccinated persons, the 4.5–7% of elderly patients with RMDs, vasculitis, dementia or stroke, have been admitted for pneumonia/influenza or death, compared to 0.8% of healthy persons (15).

While safety of non-live vaccines should be ascertained, people with systemic autoimmune diseases, such as CV, will not be able to get any of the live vaccines under development for the novel coronavirus, live virus vaccines being contraindicated in immunosuppressed people (16). It should be taken into consideration that some patients with HCV-related CV, because of their mild disease at presentation, could be treated only with DAAs without concomitant immunosuppressive agents and should therefore not be considered as immunocompromised. In these patients live-attenuated vaccines might be considered as possible when available.

To date, no specific data for SARS-CoV-2 vaccination are available and the risk of disease flare after receiving the SARS-Cov2 vaccine is unknown (17). Moreover, we may expect a reduction in the response to COVID-19 vaccination for patients taking immunosuppressive drugs or high dose of steroids, regarding both magnitude and duration of vaccine response (18-20).

Recently, it may be argued that infection with new emerging variants may carry an increased risk of hospitalisation and death, compared to infection with wild-type SARS-CoV-2 (21).

A recent study recruiting subjects receiving the BNT162b vaccine (Comirnaty) showed that the immune sera had equivalent neutralising titres to both the B.1.1.7 variant and the previous Wuhan reference strain. These data, together with the combined immunity involving humoral and cellular effectors induced by this vaccine, would make it improbable that the B.1.1.7 lineage will escape to the Comirnaty-mediated protection (22).

Finally, in the absence of conclusive data about the effectiveness of vaccination and the duration of immunisation in immunocompromised patients with CV, we suggest to complete the two-dose cycle of vaccination. Attempts to increase the number of vaccinated people using only one of two dose-vaccine have been proposed in some Countries, but they should be reserved to healthy people, or to people with previous COVID-19 (23, 24).

Apart from vasculitis itself, there are many other known priority criteria for SARS-COV-2 vaccination in cryoglobulinaemic patients, such as age older than 65, concomitant cardiomyopathy or diabetes, chronic kidney disease, liver cirrhosis, immunosuppressive treatments or concomitant glucocorticoids.

People with RMDs who contract the SARS-CoV-2 appear more likely to die from COVID-19 if their rheumatologic condition is not well controlled at the time of infection. New data from the COVID-19 Global Rheumatology Alliance (GRA) physician registry have found that the odds ratio of death for COVID-19 were 87% higher in individuals recorded as having moderate to high disease activity *versus* those reported to be in remission or having low disease activity (2).

Fragility of cryoglobulinaemic patients derives from the frequent association with vasculitis and other comorbidities and the need of long-term therapy with immunosuppressants or glucocorticoids; from these reasons, they should be prioritised for vaccination before the general population of similar age and

sex, as categorised into the extreme vulnerable group of people (25). Indeed, the risk for COVID-19 death also rose with the use of glucocorticoids. Compared with no steroid use, there was a 69% increased risk for death at doses of 10 mg or more prednisolone equivalent per day. Moreover, the Global Rheumatology Registry showed an increased risk of hospitalisation in COVID-19 patients using prednisolone dose ≥10 mg (OR 2.05) (26); therefore, it would be advisable to vaccinate patients already using a dosage below this threshold.

Therefore, WHO identified some risk factors as predictive of severe COVID-19, which have been confirmed even in patients with RMDs: age higher than 60 years, cardiovascular diseases, diabetes, hypertension, chronic respiratory diseases, immunodeficiency, and cancer (27). Furthermore, in patients with metabolic diseases, such as obesity and type 2 diabetes, the balance of innate and adaptive responses may be altered, increasing the risk of a hyperimmune response (28).

Finally, symptoms at disease onset of COVID-19 tend to be aggregated differently by age (29) and in historical cohorts, of CV patients mean age was higher than 50 and, presumably, it could be furtherly increased in the last years (30, 31).

Patients with severe COVID-19 are at increased risk of acute kidney injury, with short-term and possibly long-term loss of kidney function. At the same time, patients with chronic kidney disease, as often happens to CV patients, are at higher risk of adverse outcomes from COVID-19 (32).

In the large Open SAFELY study, mortality risk of COVID-19 patients was directly associated to the renal function and significantly increased when estimated glomerular filtration rate was lower than 30 ml/min (33).

Patients with cirrhosis have an impaired response to vaccination, explained by cirrhosis-associated immune dysfunction, and in patients with chronic liver disease, the response to vaccines is directly related to the residual liver function (34).

Despite the high number of participants in trials for COVID-19 vaccines, only few patients with mild to moderate liver disease were included and immunocompromised patients were excluded. However, up to date, among individuals already vaccinated worldwide, including patients with liver disease, no warnings on safety and effectiveness in this population have been reported (35). Recently, the European Association for the Study of the Liver stated that, despite the lack of evidence, there are no warnings on the safety and immunogenicity of currently approved vaccines in patients with chronic liver diseases, confirming the need to vaccinate this frail subgroup of patients (36).

A panel of the American College of Rheumatology (ACR) did not find the agreement for vaccination timing in patients receiving prednisone-equivalent doses ≥20mg/day, recommending no changes in therapy and vaccination timing also for high dose of prednisone (25). In patients with CV, in particular in HCV infected patients, long-term, low-dose daily glucocorticoid administration (<10 mg prednisone equivalent) seems to have a negative impact on the risk of serious infections, and can negatively affect the evolution of chronic HCV infection.

Therefore, despite the possible negative effect of glucocorticoids on vaccine efficacy, since these patients may have a worse clinical status than other rheumatic patients, steroid therapy is a priority criterion for vaccination (37).

Lymphoproliferative disease represents a frequent complication in patients with long-standing CV. There is a general agreement that onco-haematologic patients should have a priority access to COVID-19 vaccination (38).

Regarding other clinical manifestations of CV, such as neuropathy, the panel agrees that they should not influence the access criteria to vaccination.

Treatment with rituximab should be deferred of 2-4 weeks after vaccination. According to the opinion of scientific societies in patients on treatment with RTX, SARS-CoV-2 vaccination can be performed at least five months after the last RTX course.

From current knowledge, it appears that the innate immune response, and probably the subsequent anti-viral CD8 T cell responses, could eliminate the SARS-CoV2 before significant antibody response has developed. Therefore, SARS-CoV-2 would be eliminated by the majority of people with autoimmune diseases on immunotherapies, without significant consequences (39).

No data on the effects of rituximab (RTX) on COVID-19 vaccination are yet available. In patients treated with immunosuppressive medications compared to controls, the initial serologic response to pneumococcal vaccines is impaired (40). However, RTX may not interfere with pneumococcal vaccination differently from other biological agents in autoimmune diseases (41). Conversely, RTX significantly reduces humoral responses following influenza vaccination in patients with rheumatoid arthritis, with a modestly restored response 6-10 months after RTX administration (42). During COVID-19, RTX, as well as other immunosuppressive agents, rather than the disease itself, has been recently associated with the worst outcomes in RMDs (2), since it directly inhibits protective humoral immunity following infection and vaccination, but it could also indirectly affect CD4 T-cell mediated responses (43). However, B-cell targeted therapies would not influence innate and CD8 T cell responses, which are central to SARS-CoV-2 elimination. Notably, mRNA-based vaccines were shown to elicit a strong humoral response by production of neutralising antibodies, as well as a strong cellular response by inducing functional and pro-inflammatory $CD4^+$ and $CD8^+$ T cells and expression of Th1 cytokines (26, 44-47).

The EULAR 2019 guidelines recommend to vaccinate at least 6 months after the last infusion and 4 weeks before the next course of RTX, based on the state of clinical practice. Obviously, if life threatening manifestations are present, priority should be given to the treatment of vasculitis. At 2 months, an immune memory should already be stabilised so suppressing B lymphocytes would not be harmful to the immune response (48, 49).

ACR recommends to delay RTX 2-4 weeks after 2nd vaccine dose, if dis-

ease activity allows it (25). Anyway, in patients with active vasculitis, vaccination and treatment should be discussed on a case-by-case basis. Vaccination should be considered in all patients before starting immunosuppressive drugs, mainly RTX. When disease activity does not allow to delay treatment, vaccination should be always taken in account, evaluating case by case the ratio between a possible reduction in vaccine efficacy and the risk of infection by SARS-CoV-2. Except for selected cases, the steering committee suggests to always consider vaccination. Regarding the risk of worsening of the autoimmune disease due to the immune stimulus, the steering committee also retains the benefit/risk ratio in favour of vaccination (49).

It would be preferable to delay vaccination and treat the patient first with recently introduced monoclonal antibodies for COVID-19, in patients recently treated with RTX, and showing a positive swab test along with a very high disease activity.

In selected cases, SARS-CoV-2 monoclonal antibodies may be administered. They have demonstrated to reduce the risk of hospitalisation and deaths from Covid-19 by 70%. Antibodies are especially useful at the disease onset, in patients where the disease could evolve more severely. This is the case for patients with one or more risk factors such as immunodeficiencies, heart, kidney and lung disease or other comorbidities (16).

In patients treated with colchicine or hydroxychloroquine, no modification to either immunomodulatory therapy or vaccination timing is required. Methotrexate or intravenous cyclophosphamide, administration should occur preferably at least one week after each vaccine dose.

ACR provided a COVID-19 Vaccine Clinical Guidance Summary. It affirms that, when allowed by disease activity, COVID-19 vaccination should be completed at least a week before the start of immunosuppressive therapy. Glucocorticoids or immunosuppressive drugs, such as mycophenolate, azathioprine or oral cyclophosphamide should not be discontinued or modified before vaccination (25). In patients with well-controlled disease, methotrexate should be hold one week after each vaccine dose, while time of administration of intravenous cyclophosphamide should be modified, so that it will occur approximately 1 week after each vaccine dose (50).

Therapy should be continued, despite vaccination, when disease activity does not allow to reduce or discontinue immunomodulatory drugs.

There are no safety concerns for SARS-Cov2 vaccination during anti-viral therapy with direct acting antivirals (DAA) for eradicating HCV

DAAs should be viewed as the first-line treatment in HCV-related CV; adjunctive therapies are needed in most severe cases (51). A number of drug-drug interaction studies on DAAs have been conducted in both healthy volunteers and patients, but no data are available about vaccines (52). We can suppose that the mechanism of action of DAA doesn't affect the efficacy of vaccines. Moreover, some observations suggesting a possible antiviral effect of DAA against COVID-19 confirm the opportunity of maintaining treatment with DAA during vaccination course (53).

However, COVID-19 pandemic has resulted in many hepatitis elimination programmes slowing or stopping altogether. A 1-year delay in hepatitis diagnosis and treatment could result in an additional 44,800 liver cancers and 72,300 deaths from HCV globally by 2030. Countries have committed to hepatitis elimination by 2030, so attention should shift back to hepatitis programming as soon as it becomes appropriate to do so (54). Then, to mitigate the impact of COVID 19 pandemic on viral hepatitis programme and reduce excess of mortality from delayed treatment in HCV related CV, hepatitis treatment programme should be prioritised as soon as it becomes safe to do so.

Conclusions

As patients with CV could be at increased risk of infection and even worse outcomes, the importance and safety of COVID-19 vaccination is reaffirmed and further considered as a priority, especially when comorbidities are present.

However, except for some rare clinical conditions, it is always advisable to vaccinate as soon as possible. Detection of anti-spike antibodies as well as the response of T cells to the virus (55) should be suggested in patients treated with immunosuppressants for CV patients, to verify the development of an adequate immune-response.

It is reiterated that influenza and pneumococcal vaccination should be strongly considered in CV. In these patients, the risk of infectious complications is estimated to be approximately twice than general population (50, 56). Given the very recent and evolving era of discovery and widespread use of SARS-CoV-2 vaccines, the research agenda has to include the possible adverse events monitoring, the influence of immunosuppressive therapies on vaccination, the efficacy and duration of immunity response to the SARS-CoV-2 vaccine in patients with CV to further improve future vaccination programmes.

Take home messages

- Patients with cryoglobulinaemic vasculitis (CV) can be defined as fragile and a potential high risk of unfavourable outcome of SARS-CoV-2 infection and should be included among subjects to be vaccinated with priority, preferably using mRNA vaccines. Caution should be used in patients with severe, life-threatening CV. The risk of CV reactivation driven by vaccination can be supposed less relevant than the risks associated with SARS-CoV-2 infection
- Apart from vasculitis itself, there are many other known priority criteria for SARS-COV-2 vaccination in cryoglobulinaemic patients, such as age older than 65, concomitant cardiomyopathy or diabetes, chronic kidney disease, liver cirrhosis, immunosuppressive treatments or concomitant glucocorticoids.
- Treatment with rituximab should be deferred of 2-4 weeks after vaccination. According to the opinion of scientific societies, in patients on treatment with RTX, SARS-CoV-2 vacci-

nation can be performed at least five months after the last RTX course.
- In patients treated with colchicine or hydroxychloroquine, no modification to either immunomodulatory therapy or vaccination timing is required. Methotrexate or intravenous cyclophosphamide, administration should occur preferably at least one week after each vaccine dose.
- There are no safety concerns for SARS-Cov2 vaccination during anti-viral therapy with direct acting antivirals (DAA) for eradicating HCV.

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