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Position paper on the use of monoclonal antibodies against SARS-CoV-2 as passive immunisation treatments in severely immunocompromised persons in Switzerland

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Authors' statement

The authors point out that the current evidence for the efficacy of passive immunisation therapy against SARS-CoV-2 is still limited. This includes specifically its efficacy against the Omicron variant. The recommendation is also based on findings extrapolated from other risk groups than the indication group primarily addressed. We would therefore like to emphasise that passive immunisation therapy against SARS-CoV-2 should be monitored scientifically, and patient characteristics and courses should be extensively documented, preferably in patient registers.

1. Background: Why is there a need for passive immunisation therapies in Switzerland?

Immunisation is the most effective intervention to reduce the risk of severe COVID-19. Persons with severe immunodeficiency – due to inborn errors of immunity, diseases, or immunosuppressive therapies – are among the highest risk group for severe COVID-19. Immunodeficiency, however, makes this high-risk group more likely to fail to build a protective immune response to vaccination. Currently, the Federal Office of Public Health (FOPH/BAG/OFSP) and Federal Vaccination Commission (FVC/EKIF/CFV) recommend so far three doses of an mRNA vaccine and a booster vaccination after four months for severely immunocompromised patients. **Despite this intensified immunisation schedule, many of these patients fail to produce antibodies against SARS-CoV-2 and remain insufficiently protected.**

With the emergence of the Omicron variant of concern, vaccine-induced protection is substantially reduced further. **There is therefore a strong need to better protect severely immunocompromised patients.**

Other countries, including Germany (1), Austria (2), France (3), and the United States (4), are offering passive immunisation treatments to severely immunocompromised patients. Treatment with the administration of monoclonal antibodies against the SARS-CoV-2 spike protein provides good protection.

In this position paper, on behalf of the Swiss Society of Infectious Diseases (SSI), the former Clinical Care Group (CCG) of the Swiss National COVID-19 Taskforce, and the Federal Vaccination Commission (FVC/EKIF/CFV), we present the rationale for passive immunisation therapies against SARS-CoV-2 in immunocompromised patients insufficiently protected by COVID vaccines.

2. COVID-19 disease burden in immunocompromised individuals

COVID-19 mortality is substantially increased (up to 6-fold) for patients with a compromised immune system due to therapies or disease (5). The risk of severe COVID-19 depends on the type of malignancy, disease and therapy, making studies on the clinical efficacy of vaccine-induced protection for severely immunocompromised persons difficult. Although Omicron is associated with a lower mortality risk, **the protection of those who cannot be effectively vaccinated will be an important consideration.**

Mortality in hematologic malignancies has been studied in large cohorts (prior to the Omicron era). An example of available data is an analysis from the United Kingdom that included records from more than 17 million individuals associated with more than 10,000 deaths from COVID-19. Multivariate analysis showed that patients with **non-hematologic malignancy** diagnosed within one year before COVID-19 had a **1.8-fold higher risk of death** than patients without cancer, and **hematologic malignancy** was

associated with a **4-fold higher risk** (5). A higher 30-day mortality risk of 32-33% was found for both allogeneic and autologous hematopoietic cell transplantation (**HCT**) recipients. Additional risk factors included age (50 years or older [HR 2.53]), male gender (HR 3.53), development of COVID within 12 months of HCT (HR 2.67), and a diagnosis of lymphoma compared with plasma cell disorder or myeloma (HR 2.41) (6).

Similarly, **solid organ transplant (SOT) recipients** are at higher risk of severe disease when infected with SARS-CoV-2 compared with non-transplanted patients (7). Rates of hospitalisation and intensive care treatments were high before the vaccination campaign (8). Many SOT recipients are also older **and have medical comorbidities** (e.g. hypertension, diabetes mellitus, chronic kidney disease, cardiovascular disease), contributing to an high overall risk of severe COVID-19 (8). Moreover, the outcome of COVID-19 in a small case series of SOT patients with insufficient antibody titres to vaccination was comparable to unvaccinated SOT patients (9).

Finally, severe COVID-19 in subjects with a severely compromised immune system substantially prolongs the duration of intensive care unit stays, resulting in a substantial economic burden.

Conclusion: Severely immunocompromised patients are at increased risk of severe COVID-19 disease and mortality. While additional measures are still needed to protect this very vulnerable population, passive immunisation may add an additional layer of security and allow these patients some activities otherwise not possible.

3. Impaired SARS-CoV-2 vaccine responses in immunocompromised persons

Severely immunocompromised individuals are less likely to respond to vaccination, meaning they produce fewer or no antibodies in response to repeated vaccine doses. In the absence of a humoral immune response, this risk group is less well protected against COVID-19. Since the now-dominant Omicron variant substantially escapes the vaccine-induced antibody responses, protection may be even lower, urging immediate measures to better protect this high-risk group.

The extent to which the immune response to SARS-CoV-2 vaccination is attenuated depends on the underlying condition and type of immunosuppressive treatment. Vaccine non-response refers to the absence or only minimal presence of antibody production after vaccination. Data, including from Swiss studies, on the failure to generate protective immunity have shown that serological absence of antibody production does not rule out the possibility that the individual may mount robust T cell responses (10-12). Data in B-cell-depleted multiple sclerosis patients indicate good T-cell responses in many (10-12). However, epidemiological data on the level of clinical protection these T cells provide are currently lacking.

Data for different immunocompromised patient groups have recently been summarised in a systematic review (13). Vaccine non-responder rates were relatively high in populations with cancer (2-36%) and haematological malignancy (14-61%). The highest non-response rate was seen in patients treated with **cytotoxic chemotherapy, Bruton tyrosine kinase inhibitors (BTKi), anti-CD20 treatment (e.g. rituximab) or anti-CD38 (daratumumab)-based regimens** (13). In solid cancer, non-response rates were highest in patients undergoing active treatment at the time of vaccination.

Among patients with **haematological malignancies**, non-response rates were highest for **chronic lymphocytic leukaemia (28-77%)** and **lymphoma (30-58%)** (13), especially if recently treated with a B-cell depleting agent (14). Patients with multiple myeloma (5-34%) and myeloproliferative neoplasms (e.g. CML) (12-20%) displayed lower rates of non-response. Similarly, HCT was associated with non-response rates ranging from 14% to 31% in **allogeneic HCT,** and mostly maintained response rates in autologous HCT (13).

Almost fifty studies have assessed immunogenicity in **solid organ transplantation** (59% kidney transplant). Non-response rates ranged from 18% to 100% depending on the transplant setting, with 35-98% in kidney transplant, 19-63% in liver transplant recipients, 25-88% in heart transplant recipients, and 59-100% in lung transplant recipients (13). Specific treatment regimens especially compromised the vaccine response (i.e., calcineurin inhibitors, antimetabolites [e.g., mycophenolate-mofetil], and corticosteroids), age, and kidney function (13).

In patients on haemodialysis, the vaccine non-response rate was lower (ranging from 2% to 5% in four studies rated as ‘good quality’) (13). However, there appears to be a high proportion of patients achieving only low antibody levels (13).

Among **inflammatory immune-mediated diseases** such as rheumatoid arthritis, inflammatory bowel disease and multiple sclerosis, non-response rates ranged from 0% to 63%. Patients treated with **B-cell-depleting therapies** (e.g. rituximab and ocrelizumab) were at the highest risk of antibody non-response. Methotrexate, systemic corticosteroid therapy and other non-biological, immunosuppressive therapies have been associated with reduced antibody levels (15, 16).

Two studies assessed immunogenicity in patients with **inborn errors of immunity** (mostly common variable immunodeficiency) and reported non-response rates of 23% and 27% (13).

Conclusion: A specific patient group – defined by diagnoses or treatment modalities – has a high risk for SARS-CoV-2 vaccine non-response, leaving these patients insufficiently protected from severe

COVID-19. The same group is overrepresented among severe COVID-19 cases, highlighting the urgent need to improve the protection of this vulnerable population.

4. Criteria for eligibility for passive immunisation and estimated burden of disease

In 2021, the Swiss Society for Infectious Diseases (SSI) and the former Clinical Care Group (CCG) of the Swiss National COVID-19 Science Task Force had established recommendations for the use of monoclonal antibody therapies in treatment settings (17). Patients were classified according to the high risk of disease progression (high-risk group according to the FOPH (BAG/OFSP) categories of persons at particular risk). **The most vulnerable patients (to be prioritised) include patients with diseases/therapies that weaken the immune system (FOPH/BAG/OFSP list, criterion 5)**.

In the **absence of broadly available monoclonal antibodies** for passive immunisation therapy, **priority** should be given to a defined highest-risk group. These criteria include (i) presence of one of the defined medical conditions (Priority Group in Table 1) and (ii) the absence (or near absence) of anti-S-IgG after SARS-CoV-2 vaccination in accordance with current recommendations (FOPH [BAG/OFSP] /FVC [EKIF/CFV]) recommendations for mRNA vaccines against COVID-19). Notably, for severely immunocompromised individuals, post-exposure antibody therapy may be available in case of infection (17). As soon as **monoclonal antibody** products for passive immunisation therapy are broadly available, the indication can potentially be extended to all high-risk groups according to the FOPH (BAG/OFSP) categories of persons at particular risk for severe COVID-19 (besonders gefährdete Personen [BGP], personnes vulnérables [PV]) depending on the epidemiology and the ongoing evaluation of available data.

Table 1: Highest priority group for passive immunisation therapy based on immunocompromising high-risk conditions for severe COVID-19

- Severe immunosuppression (e.g. HIV infection with a CD4+ T-cell count <200/µl)
- Active chemotherapy for cancer*
- Patients with chronic neutropenia (<1,000 neutrophils/µl)
- Hereditary immunodeficiencies (inborn errors of immunity; including CVID)
- B-cell-depleting therapies, combination immunosuppressive therapies (particularly with long-term use of glucocorticoids >20mg prednisone equivalent/d)
- Haematological malignancies (e.g., leukaemia, lymphoma, GVHD; including HSCT and CAR-T, multiple myeloma, myeloproliferative diseases)
- Solid organ transplantation

CVID = common variable immunodeficiency; GVHD= graft vs host disease; HSCT= haematological stem cell transplant; CAR-T= chimeric antigen receptor T cells. *At the time of primary vaccination against COVID, and no option of re-vaccination. Adapted from (17).

Table 2: Estimated number of highest-risk immunocompromised patients in Switzerland.

Underlying condition/therapy	Estimated number of affected persons living in Switzerland
SOT	2,000
Active chemotherapy for cancer* and haematological malignancies (e.g. CLL, MM, leukaemia, lymphoma, GVHD; including HSCT and CAR-T)	2,000-3,000
B-cell-depleting therapies for MS, RA, etc.	3,000-5,000
Inborn errors of immunity (CVID, WAS, SCID…)	500
HIV-infected subjects with CD4+ T-cell count <200/µl and detectable HIV RNA	50

SOT= solid organ transplant; CLL= chronic lymphatic leukaemia; MM= multiple myeloma; GVHD= graft vs host disease; HSCT= haematological stem cell transplant; CAR-T= chimeric antigen receptor T cells; MS= multiple sclerosis; RA= rheumatoid arthritis; CVID = common variable immunodeficiency; WAS= Wiskott Aldrich syndrome; SCID = severe combined immunodeficiency. *At the time of primary vaccination against COVID, and no option of re-vaccination.

Conclusion: The patient group that would qualify for passive immunisation therapy in Switzerland can be **well defined, is typically in a highly specialised treatment setting (university or cantonal hospital) and will be limited to about 10,000 persons** in Switzerland.

5. Efficacy of monoclonal antibodies against SARS-CoV-2

Monoclonal antibodies are laboratory-made immunoglobulins targeting a specific protein region in a pathogen. Currently available monoclonal antibodies against SARS-CoV-2 in Switzerland include casirivimab/imdevimab and sotrovimab. AstraZeneca's monoclonal antibodies (Evusheld®, formerly known as AZD7442) are not yet currently available in Switzerland, but are the first FDA-approved monoclonal antibodies for passive immunisation therapy. On 23 March 2022 the EMA recommended authorization of Evusheld® for the prophylactic therapy/immunisation.

In December 2021, the SARS-CoV2 Omicron variant emerged, which contains many mutations in the spike protein that affect recognition by antibodies and increase the infectivity of the virus (18). These characteristics are highly relevant for the selection of passive immunisation therapy. Considerations for the optimal mAb have been considerably complicated due to the Omicron wave – most marketed mAbs have completely, or partially, lost efficacy (19). Currently there are no study results available on the

clinical treatment effect of mAbs on infections with the Omicron variant. We will therefore use the SSI/ former CCG registry to monitor patients' clinical and virological outcomes.

Ronapreve® (casirivimab/imdevimab) combines two recombinant human mAbs that bind to non-overlapping epitopes of the spike protein RBD of SARS-CoV-2. The treatment outcomes of this antibody combination in outpatients with COVID-19 showed a 70.4% relative risk reduction for hospitalisation or death at day 28 (20). Subcutaneous casirivimab/imdevimab antibody combination, which was studied to prevent COVID-19, showed a relative risk reduction against symptomatic SARS-CoV-2 infection of 81.4% for SARS CoV-2 (21). **However, casirivimab/imdevimab shows no efficacy against the Omicron variant *in vitro* (18, 22, 23). Therefore, it cannot be considered for passive immunisation treatment during the Omicron wave.**

Xevudy® (sotrovimab) is a monoclonal antibody initially identified in a SARS-CoV-1 survivor in 2003. It targets an epitope in the RBD of the spike protein conserved between SARS-CoV and SARS-CoV-2. Early treatment of COVID-19 with the SARS-CoV-2 neutralising antibody sotrovimab showed a relative risk reduction of 85% for hospitalisation or death at day 28 (24). In-vitro studies demonstrated reasonable Omicron (BA.1) neutralisation of sotrovimab, possibly owing to its binding outside the receptor-binding motif (18, 22, 25). However, additional mutations of the spike protein in the Omicron sub-lineage BA.2 render the virus more resistant to neutralisation by sotrovimab. The maintained partial Omicron neutralisation was only observed for sotrovimab and the monoclonal antibodies from AstraZeneca (tixagevimab/cilgavimab; see below), while the other commercially available mAbs showed no neutralising capacity against Omicron (23, 26).

Evusheld® (AZD7442, tixagevimab/cilgavimab) consists of two monoclonal IgG1 antibodies targeting two different, non-overlapping epitopes of the spike protein receptor-binding domain (RBD) of the SARS-CoV-2 virus. By interfering with the interaction within the RBD of the spike protein with the ACE2 receptor on cells, they prevent the virus from entering a cell (i.e. block infection). The antibodies in tixagevimab/cilgavimab are modified in the Fc region to reduce degradation and prolong half-life, allowing dosing every six months. The efficacy of tixagevimab/cilgavimab was assessed in the Phase III PROVENT trial, demonstrating that a single injection provided about 80% protection against symptomatic COVID-19 for at least six months. Subjects at high risk for severe COVID-19 (n=5197, mainly persons >60 years of age and with co-morbidities) were randomised 2:1 to a single administration of two injections with 150 mg tixagevimab and 150 mg cilgavimab or placebo injected i.m. The intervention group had a significant reduction of symptomatic COVID-19 (PCR test confirmed) over more than six months (median follow-up 196 days; no trend of decreased efficacy) (AZ press release; FDA documentation).

The PROVENT study was performed before the emergence of the Omicron variant. To date there have been no in-vivo efficacy data available for the preventive treatment against Omicron. Several studies have addressed the neutralising capacity of the AZD7442 antibodies (tixagevimab/cilgavimab). AZD7442 consistently showed good neutralisation of the delta variant. Tixagevimab alone (26) (https://www.medrxiv.org/content/10.1101/2021.12.14.21267772v1) or the AZD7442 antibody combination (22, 23, 27, 28) neutralised the Omicron variant in pseudo-virus neutralisation assays. The *in vitro* neutralisation against the omicron BA.1 strain was lower compared with sotrovimab (27). Independent testing in the FDA's Center for Biologics Evaluation and Research (FDA approval documents) confirmed that the combination of tixagevimab/cilgavimab retains neutralisation activity against Omicron in the range observed in convalescent COVID-19 patients (ACTIV. National Center for Advancing Translational Sciences OpenData Portal. SARS-CoV-2 Variants & Therapeutics, All Variants Reported in vitro therapeutic activity (available at: https://opendata.ncats.nih.gov/variant/activity)). In addition, in vitro data show higher neutralisation activity for Omicron/BA.2 compared to Omicron/BA.1 (29, 30). One study investigated the neutralisation capacity of sera obtained from subjects receiving Evusheld®. They observed neutralization of BA.1 and BA.2 in 19/29 and 29/29 Evusheld® recipients, respectively. Compared to delta neutralization, the neutralizing serum titers were about 344-fold reduced against BA.1 (344-fold), but only 9-fold reduced against BA.2 (31).

Conclusion: Since the Omicron variant accounts for >99% of the isolates tested in Switzerland (April 2022) and based on availability, the **current monoclonal antibody of choice for preventing severe COVID-19 would be Evusheld®, owing to its partial capacity to inhibit Omicron (at least the currently most dominant sub-lineages, BA.1 and BA.2).**

6. Availability and approval of monoclonal antibodies against SARS-CoV-2 in Switzerland

As of 26 January 2022, two monoclonal antibodies have received at least temporary approval by Swissmedic for the treatment, and one also for prevention of COVID-19.

6.1 Ronapreve® (casirivimab/imdevimab)

On 23 December 2021, Ronapreve®, a combination of the two monoclonal antibodies casirivimab and imdevimab, was approved for SARS-CoV-2-infected patients (>12 years old) with high risk for severe COVID-19 who are not yet in need of oxygen therapy or hospitalisation.

As a second indication, Ronapreve® can also be given prophylactically in patients with inadequate immune response to COVID-19 vaccination. It was therefore the first drug authorised by the Swiss regu-

lator for the prevention of COVID-19 in cases where there is no sufficient immune response after vaccination owing to other diseases or treatments. Ronapreve® is given as a single intravenous infusion or subcutaneous injection. **Given that Ronapreve® is ineffective against the Omicron variant, it cannot be used as passive immunisation therapy**.

6.2 Xevudy® (sotrovimab)

Swissmedic has granted temporary authorisation for Xevudy® (sotrovimab, **link**) to treat COVID-19 in adults and adolescents aged 12 years and over on an outpatient basis if they have a high risk of developing a severe form of COVID-19. Xevudy® is currently not approved for use before a SARS-CoV-2 infection is confirmed.

6.3 Evusheld® (AZD7442, tixagevimab/cilgavimab)

The FDA approved Evusheld® for persons not currently infected with SARS-CoV-2 with moderate to severe immunosuppression, who may not mount an adequate immune response to COVID-19 vaccination. In addition, it can be given to persons for whom vaccination with the available COVID-19 vaccines is not recommended owing to a history of severe adverse reactions. Evusheld® is currently under a rolling review for authorisation by the EMA. On March 23 2022 the EMA authorised Evusheld® for the prophylactic therapy. In France, the HAS (Haute Authorité de Santé) authorised Evusheld® as a passive immunisation treatment for high-risk groups on 10 December 2021 (https://www.has-sante.fr/jcms/p_3304034/fr/evusheld-tixagevimab/cilgavimab). Since 10 February 2022 Evusheld® is under review for authorization in Switzerland.

7. Current recommendations or use of passive immunisation therapy in other countries

Several countries have already implemented passive immunisation therapy for high-risk groups. A position paper from **France** (3) recommends passive immunisation in **immunocompromised patients** who are unable to build up an **antibody titre > 264 BAU/ml** 4 weeks after the fourth vaccination dose.

The German position paper (1) recommends passive immunisation in **immune compromised patients** not capable of mounting an antibody titre **above 0 BAU/ml** four weeks after the fourth vaccination, or who are not fully vaccinated with any available SARS-CoV-2 vaccines owing to a documented history of severe adverse reaction to a SARS-CoV-2 vaccine or any of its components.

Similarly, the National Institute of Health (NIH) guidelines (4) recommend passive immunisation with tixagevimab/cilgavimab for individuals who are moderately to severely immunocompromised and who may have **inadequate immune response to COVID-19 vaccination**, or who are not fully vaccinated

with any available SARS-CoV-2 vaccines owing to a documented history of severe adverse reaction to a SARS-CoV-2 vaccine or any of its components.

Conclusion: Various countries have implemented passive immunisation therapies. The indications vary, but also restrict access to high-risk immunocompromised patients with a very low or non-existent immune response to vaccination and who are therefore well in line with our position paper. The more restrictive criteria proposed here will be adapted once monoclonal antibody therapies become more widely available and are approved for passive immunisation therapy.

8. Proposal (algorithm) for selection criteria for passive immunisation treatment

The indication for passive immunisation therapy is primarily given to patients who belong to the high **priority group** listed in **Table 1** who, in addition, fulfil one of the following criteria:

(i) Failed to mount an anti-Spike-IgG antibody response (i.e. an absent or nearly absent antibody test) after vaccination with at least three doses of a SARS-CoV-2 vaccine approved in Switzerland (preferably an mRNA vaccine), and a fourth dose is not expected to increase the antibody level. The antibody titre should be measured within four weeks after the last vaccine dose.

or

(ii) Who cannot be vaccinated owing to their inability to establish vaccine protection due to allogeneic HCT, CAR-T therapies, or B-cell-depleting therapies in the previous < 3 months.

If the **availability of passive immunisation treatment products allows**, the indication is extended to a broader **group**. The second priority group includes all patients with severe immunosuppression who have not developed a good anti-spike IgG antibody response (defined as <264 BAU/ml) after four doses (or 3 doses in those with confirmed SARS-CoV-2 infection at least 4 months apart) of a SARS-CoV-2 vaccine (preferably an mRNA vaccine) licensed in Switzerland. The third priority group includes all persons belonging to all other risk groups for severe COVID-19 (i.e. all BGP/PV) who failed to mount a good antibody response. Within this group, those without antibodies after vaccination (0 BAU/ml) should be prioritised during shortages of available antibody doses.

The priorisation aims to ensure that those persons with the strongest need will have priority access. There will always be situations in which the criteria may not be fulfilled, but there is a strong assumption that the person will benefit from passive immunisation. The decision about access to the monoclonal antibody in such cases should be discussed and made by the responsible multidisciplinary team.

The recommended d**osage for passive immunisation therapy, AZD7442 (Evusheld®) as an i.m. administration** is **300 mg of Evusheld**, as 150 mg of tixagevimab and 150 mg of cilgavimab administered as separate sequential intramuscular injections based on the results on the phase 3 registrational trial, the PROVENT study. A **higher dose of 600 mg of Evusheld**, as 300 mg of tixagevimab and 300 mg of cilgavimab, given as two separate, sequential intramuscular injections, is more appropriate for some SARS-CoV-2 variants (for example, Omicron BA.1, Omicron BA.1.1, BA.2) based on in vitro neutralisation susceptibility data which show reduced susceptibility for Evusheld. The dosing of 300mg of each monoclonal antibody is higher than in the phase III preventive trial. The high dose has recently been FDA approved based on a predicted better protection from Omicron variants and safety data from a treatment trial with Evusheld® using the same dosing. This high dose is also recommend for the above mentioned SARS CoV-2 variant in the USA, France and UK. AZD7442 (Evusheld®) at either dosage should be repeated every six months for as long as SARS-CoV-2 circulates. Indications for all passive immunisation treatments should be assessed by an infectious disease specialist, and application should be limited to specialised patient care centres (university hospitals and cantonal hospitals).

We aim to ensure equity in access to treatment for all those who qualify for such a treatment, regardless of the canton, the hospital or the prescribing physician.

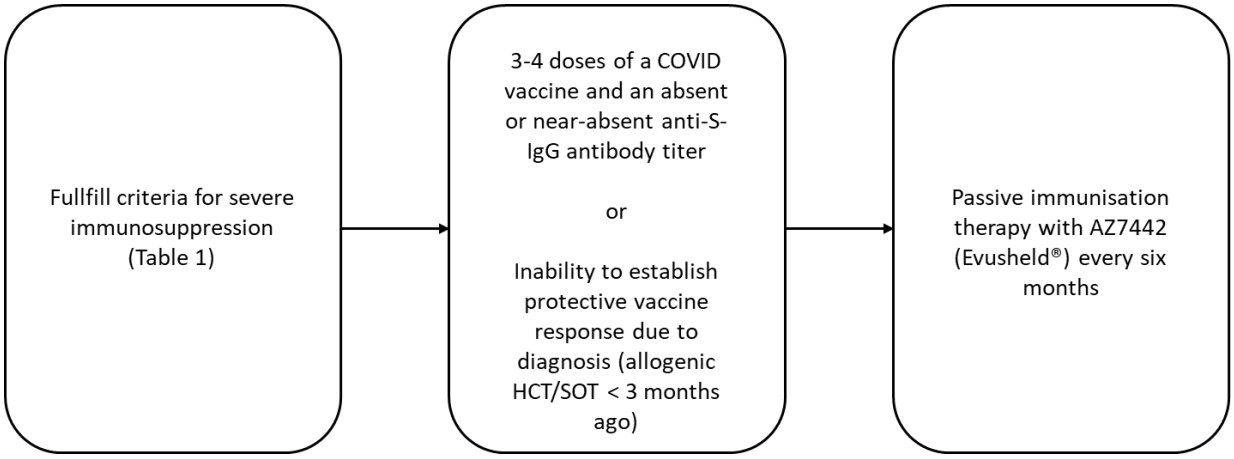

Figure 1: Suggested treatment criteria

9. Cost justification

Patients with a compromised immune system are at the highest risk of severe COVID-19 and its complications, because they cannot build up immune protection after vaccination. The risk will also depend on the epidemiological situation. Since all subjects covered by our recommendation are at high risk of severe COVID and have failed to build a strong serological immune response, it can be assumed that the number needed to treat (NNT) to prevent one severe case might be lower than in the published

studies that also included subjects with a lower risk of severe COVID. Therefore we would expect the financial cost of one prevented ICU admission (CHF >250,000) to outweigh the costs of covering passive immunisation therapies for several at-risk individuals. Passive immunisation is already the standard of care against other pathogens for many high-risk patients (stem cell transplant/primary immunodeficiencies) with the administration of polyclonal immunoglobulins (IVIG) or pathogen-specific immunoglobulins in high-risk situations (e.g. measles or varicella outbreaks). The at-risk groups discussed here are often parents of younger children, and entire families are subjected to extreme limitations to protect themselves from hospitalisation/deaths during this pandemic.

10. Epidemiological considerations

Owing to the current SARS-CoV-2 epidemic, where the Delta and Omicron variants have unprecedented incidence rates in Switzerland, the demand is urgent. When the epidemiological situation is less urgent, the use of monoclonal antibodies could be limited again to the early post-exposure or early empiric treatment, i.e. for patients tested positive and at a high risk of severe COVID-19. Of note, any emergence of a new variant and/or sub-lineage may require choice of treatment to be changed.

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