Response to COVID-19 vaccination and COVID-19 infections after vaccination in patients with haematological malignancies

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO) [1].
Type of Research Project:	Research project involving human subjects
Risk Categorisation:	Risk category A according to ordinance HRO Art.7

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PROTOCOL SIGNATURE FORM

Study Title:

Response to COVID-19-vaccination and COVID-19-infections after vaccination in patients with haematological malignancies

The project leader has approved the protocol version 1.0 (10.05.2021) and confirms hereby to conduct the project according to the protocol, the Swiss legal requirements [1, 2], current version of the World Medical Association Declaration of Helsinki [3] and the principles and procedures for integrity in scientific research involving human beings.

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GLOSSARY OF ABBREVATIONS

BAG	*Bundesaamt für Gesundheit*
BASEC	*Business Administration System for Ethical Committees*
CRF	*Case report form*
COVID-19	coronavirus disease 2019

FOPH	*Federal Office of Public Health*
HRA	*Human Research Act*
HRO	*Ordinance on Human*
SARS-CoV-2	severe acute respiratory syndrome coronavirus type 2

1 BACKGROUND AND PROJECT RATIONALE

The prevalence and mortality of COVID-19 are higher in patients with haematological malignancies (HM) compared to the general population (Vijenthira et al. 2020). Two SARS-CoV-2 messenger RNA (mRNA) vaccines have been approved by Swissmedic, both are highly efficient in preventing COVID-19 in the general population. The efficacy of these vaccines in patients with haematological malignancies remains unknown as immunocompromised patients have been excluded from the vaccine studies.
Initial reports on immunocompromised patients, such as solid organ transplant recipients, indicate a lower immunogenicity in immunocompromised hosts with only 11% to 17% having detectable anti-spike antibody 20-28 days after one vaccine dose (Boyarsky et al. 2021).

With regard to patients treated at the Cantonal Hospital St. Gallen, 7 of 66 myeloma-patients vaccinated against COVID-19 since January 2021 suffered from a COVID-19 infection despite having received one or two vaccinations against COVID-19. Two patients died. This indicates a clinically relevant suboptimal response to the current vaccines in at least a subgroup of patients with haematological malignancies. However, it is largely unknown, which kind of diseases and treatments are associated with a less effective vaccination response.

In general, in patients with haematological malignancies, the potential benefit of applying available anti-viral vaccines is considered to outweigh the risk (Cheuk 2011). However, there is clear evidence for an insufficiency of the respective vaccines in a variety of conditions. Especially B-cell depleting therapies and probably B-cell malignancies itself seem to weaken the humoral vaccination response (Sun et al. 2021). The anti-CD20 antibody Rituximab, widely used in the treatment of B-cell malignancies, has been shown to render vaccinations against Influenza A widely ineffective (Berglund et al. 2014). Hence, some medical societies recommend against influence-vaccinations during treatment with Rituximab (Rieger et al. 2018). However, B cell depletion may not preclude a cellular vaccination response totally: in a study regarding the efficacy of a recombinant varicella zoster (VZV) vaccine, 50% of patients who did not seroconvert showed a T-cell response against VZV (Zent et al. 2020). Anti-CD38-antibodies like Daratumumab are now widely used in the treatment of myeloma patients. Treatment with Daratumumab is known to alter the T-cell compartment in myeloma patients (Krejcik et al. 2016). Hence, T-cell responses after COVID-19-vaccination may be impaired as well during Daratumumab treatment. Of note, five of the seven of our patients with a COVID-19 infection after vaccination were treated with Daratumumab.

2 PROJECT OBJECTIVES AND DESIGN

2.1 Hypothesis, primary and secondary objectives

The hypothesis of the presented project is that the response to SARS-CoV-2 vaccination is impaired in at least a subgroup of patients with haematological malignancies.

We hypothesize that the response to SARS-CoV-2-vaccination is impaired either by the disease itself, since haematological malignancies arise in cellular components of the innate or adoptive immune system or by the treatments applied, since nearly all compounds used to treat haematological neoplasms may be associated with immunosuppressive side effects.

2.2.1 Primary objectives
To assess the efficacy of the approved SARS-CoV-2 vaccination in patients with haematological malignancies by documenting:

1. The humoral response by measuring the titre of anti-spike antibodies
2. The cellular response by measuring SARS-CoV-2-specific T-cells
3. The rate and outcome of COVID-19 occurring in patients with haematological malignancies after vaccination (i.e. having received at least on dosage)

2.2.2 Secondary objectives

1. To identify characteristics of the underlying disease (type of haematological neoplasm, stage, newly diagnosed or relapsed, extent of disease-associated immunosuppression, comorbidities, laboratory parameters such as full blood count, cellular immune status, titre of immunoglobulins) which are associated with a suboptimal vaccination-response

2. To identify mode of treatments for haematological malignancies (type of treatment as conventional chemotherapy, antibodies, small molecules, amount of steroids applied), which are associated with a suboptimal vaccination-response

3. To characterize severity and course of COVID-19 occurring in patients with haematological malignancies despite vaccination

2.2 Primary and secondary endpoints

Primary endpoints
Rate of patients without seroconversion after vaccination
Rate of patients developing COVID-19 despite vaccination

Secondary endpoints
Rate of patients without detectable SARS-CoV-2-specific T-cells after vaccination
Rate of patients with asymptomatic COVID-19 despite vaccination
Rate of patients with COVID-19 despite vaccination in need of hospitalisation
Rate of patients with COVID-19 despite vaccination in need of ventilation support

2.3 Project design

This is a prospective non-randomized exploratory cohort study. It is designed as a pilot project and should be hypothesis generating for further research focusing on the efficacy of COVID-19 vaccines in patients with haematological neoplasms.

3 PROJECT POPULATION AND STUDY PROCEDURES

The majority of cancer patients treated at our institution has received two vaccinations against COVID-19 since January 2021. Patients newly diagnosed, will be vaccinated as well.

Patients with haematological malignancies represent the target population. According to the frequency of disease entities treated at our institution, patients with multiple myeloma (target patient number 80), chronic lymphocytic leukaemia (target patient number 40) and myeloproliferative neoplasms (target number n=30) represent the major subgroups. Patients with less frequent disease will be included as well, even if the results may be only hypothesis generating due to the low patient number.

3.1.1 Inclusion Criteria

- Documented haematological neoplasm belonging to one of the following groups, irrespective of stage and current treatment:
  - Multiple Myeloma
  - Chronic lymphocytic Leukaemia

- Hodgkin-Lymphoma
- Non-Hodgkin-Lymphoma
- Acute Myeloid Leukaemia
- Acute Lymphoblastic Leukaemia
- Myelodysplastic Syndrome
- Myeloproliferative Neoplasm
- Myelodysplastic/Myeloproliferative Neoplasms

- Patients must have either already received vaccination against COVID-19 with any of the approved compounds or are planned to be vaccinated at time of enrolment into this study.
- Patients must have given informed consent

3.1.2 Exclusion criteria

- Any concomitant medical conditions, not related to the haematological neoplasm, which is known to be associated with an immunosuppression (e.g. HIV infection, solid organ transplantation with need for immunosuppressants, active autoimmune-disease)
- Any immunosuppressive treatment given for diseases other than the haematological neoplasm.
- Previous documented infection with SARS-CoV-2 before enrolment in this study, defined as SARS-COV-2 PCR or antigen positive and/or related symptoms and documented serovonversion

3.2 Recruitment, screening and informed consent procedure

Patients will be recruited at the Cantonal Hospital St. Gallen. Recruitment will take place on the basis of daily clinical practice. Irrespective of current treatment, patients will be informed about the project and asked if they are willing to participate and have drawn additional blood samples for research purposes. No financial compensation will be given to participants. If patients give consent for participation, they will undergo screening procedures, i.e. check of patient records for co-morbidities and conditions resembling an exclusion criterion.

3.2 Study procedures

3.3.1 Aspiration of peripheral blood and laboratory analyses

Participants will undergo an aspiration of approx.10-20 ml peripheral blood at the respective visits. The blood samples will be analyzed for the following parameters according to the following schedule

3.3.2 Schedule of assessments for patients already being vaccinated before study inclusion:

	Baseline	month 3, 6 and 12
anti-Nucleocapsid-Antibodies	X	X
Anti-spike antibodies	X	X
SARSC-CoV-2-specific T-cells	X	X
Immune status by flow-cytometry	X	X
Serum IgG (incl. subclasses), IgM, IgA	X	X
Free light chains	X	X

Serum sample for cytokine measurements	X	X

3.3.3 Schedule of assessments for patients being vaccinated after inclusion into the study

	Vaccination1	10-14 days after Vaccination 1	Vaccination 2	21 days after vaccination 2	Months 3,6 and 12 after first vaccination
anti-Nucleocapsid-Antibodies	X	X	X	X	X
Anti-spike antibodies	X	X	X	X	X
SARSC-CoV-2-specific T-cells	X	X	X	X	X
Immune status by flow-cytometry	X	X	X	X	X
Serum IgG (incl. subclasses), IgM, IgA	X	X	X	X	X
Free light chains	X	X	X	X	X
Serum sample for cytokine measurements	X	X	X		

3.3.4 Schedule of assessments for patients receiving a third Vaccination according to the recommendations of the “Bundesamt für Gesundheit (BAG), issued on July 21th, 2021:

	Before third vaccination	1 month after third	3 months after third vaccination	6 months after third vaccination	12 months after third vaccination
anti-Nucleocapsid-Antibodies	X	X	X	X	X
Anti-spike antibodies	X	X	X	X	X
SARSC-CoV-2-specific T-cells	X	X	X	X	X
Immune status by flow-cytometry	X	X	X	X	X
Serum IgG (incl. subclasses), IgM, IgA	X	X	X	X	X
Free light chains	X	X	X	X	X
Serum sample for cytokine measurements	X	X	X		

3.3.2 Collection of clinical data, including side effects of the vaccination

For all patients, data regarding the haematological neoplasm and the treatment history will be collected from clinical records, as will be data regarding side effects of the vaccination

For patients developing COVID-19 after having received at least one vaccination dose, clinical data regarding the infection (e.g. symptoms, hypoxia, hospital admission, need of oxygen supply or ventilation support, treatments applied, duration of hospital stay including those on the intensive-care-unit, need of rehabilitation, development of a post COVID-syndrome) will be collected from hospital records.

3.4 Withdrawal and discontinuation

Patients can withdraw from the study at any time without providing reasons. If patients allow to use the data and biological samples already obtained until consent withdrawal, the respective data will be analysed.

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

Levels of anti-Spike-antibodies and numbers of SARS-CoV-2-specific T-cells will be described by measures of standard descriptive statistics (median, median, range) and compared between different patients groups by the Mann-Whitney (comparison of two groups) or the or the Kruskal-Wallis-Test (comparison of three or more groups). The association of categorial variables with an insufficient response to vaccination will analysed by cross tables and compared by the χ^2-Test.

In order to compare the vaccination responses achieved by patients with haematological neoplasms to those achieved in a healthy population, data from the ongoing “SURPRISE” and “Corona-Immunitas”-Studies will be accessible.

With regard to the effect of different treatments on the SARS-CoV-2 vaccination, the comparison of the following patient groups is intended for a first explanatory analysis:

Myeloma	Anti-CD38-antibody based regimen versus no CD38-Antibody
Chronic Lymphocytic Leukemia	Anti-CD20-antibody-containing regimen versus no CD20-antibody Bruton-Tyrosin-Kinase-Inhibitor-based treatment versus Venetoclax-based treatment
Non-Hodgkin-Lymphoma	Rituximab-CHOP versus Rituximab-Bendamustin based treatment
Myeloproliferative Neoplasms	BSC versus Hydroxurea-based treatment versus JAK-Inhibitor-based treatment versus Interferon
Myelodysplastic syndromes	BSC versus Hypomethylating agents versus Lenalidomid
Hodgkin Lymphoma	BEACOPPescalated versus ABVD

Data analysis will be performed by using standard software packages (SPPS; R, Stata).

4.2. Handling of missing data

All data will be checked for completeness and consistency. Where possible, it will be attempted to correct all errors detected in the data with the help of the responsible physician. If possible, imputation may be used on certain variables. Any changes, omissions and additions to the data as a result of these processes will be reported.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki [3], the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) [1] as well as other locally relevant regulations. The Project Leader acknowledges his responsibilities as both the Project Leader and the Sponsor.

5.2 Notification of safety and protective measures (HRO Art. 20)

The project leader is promptly notified (within 24 hours) if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified via BASEC of these measures and of the circumstances necessitating them within 7 days.

5.3 Serious events (HRO Art. 21)

If a serious event occurs, the research project will be interrupted and the Ethics Committee notified on the circumstances via BASEC within 7 days according to HRO Art. 21[1].

5.4 Procedure for investigations involving radiation sources

Not applicable

5.5 Amendments

Substantial changes to the project set-up, the protocol and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 before implementation. Exceptions are measures that have to be taken immediately in order to protect the participants.

5.6 End of project

Upon project completion or discontinuation, the Ethics Committee is notified within 90 days. All biological materials and health-related data are anonymized upon termination of data analysis.

5.7 Insurance

In the event of project-related damage or injuries, the Sponsor will be liable, except for damages that are only slight and temporary; and for which the extent of the damage is no greater than would be expected in the current state of scientific knowledge (Art. 12 HRO).

6 FURTHER ASPECTS

6.1 Overall ethical considerations

[1] A serious event is defined as any adverse event where it cannot be excluded, that the event is attributable to the sampling of biological material or the collection of health-related personal data, and which:
a. requires inpatient treatment not envisaged in the protocol or extends a current hospital stay;
b. results in permanent or significant incapacity or disability; or
c. is life-threatening or results in death.

During the ongoing COVID-19-pandemic, patients with hematological malignancies represent a very vulnerable patient group, bearing a higher risk for both acquiring the infection and suffering a more severe cause of disease including death.

Vaccination is considered as one of the cornerstones to overcome the current COVID-19 pandemic. However, little is known about the efficacy of the current vaccinations in immunocompromised patients. Hence, this project deals with a highly relevant unmet clinical need, since it addresses the question, whether patients with hematological malignancies are sufficiently protected from SARS-CoV-2-infections by the current vaccines.

Results of the project will be especially helpful, if a patient population is identified, in which the current vaccination strategies are insufficient. These patients could profit from further advice about proper security measures e.g. prolonged use of personal protective equipment such as masks and hand hygiene even after vaccination and the recommendation to vaccinate close contact persons. Moreover, booster vaccinations might be considered and studied further for this patient population. If a particular form of treatment should turn out to interfere with the vaccination response, strategies to adapt treatment until a sufficient vaccine response is achieved could be developed.

6.2 Risk-Benefit Assessment

Since the only study-specific intervention will be additional blood draws, which represent a routine procedure in daily clinical practice, participants are not subjected to any substantial risk.

Remaining minor risks include:

- Haematoma formation at the puncture site (rarely clinically significant).
- Local pain.
- Rarely local infection.

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

Several procedures guarantee quality of conduct of the project:

- Reviews of protocol and consent forms according to standard operating procedures
- Statistical analyses will be used when evaluating the data
- An authorization list must be kept at the centre
- All project specific procedures are performed according to the safety SOPs of the Clinical Trials Unit.

7.2 Data recording and source data

The data will be collected electronically using SecuTrial®. Source data include the Clinical Information System used at the Cantonal Hospital St. Gallen (“PMS”) and the clinical information system of the Zentrum für Labormedizin St. Gallen (“INLAB”)

7.3 Confidentiality and coding

Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the CRFs and other project specific documents, participants are only identified by a unique participant number.

Patient samples and data are obtained, stored and used following the guidelines and recommendations of the Swiss Academy of Medical Sciences (SAMS) on biobanks ("Biobanks: obtainment, preservation and utilisation of human biological material", 2006). Samples are coded reversibly, and access to personal data is only possible with a key to the sample code, which is stored and managed separately from the data following the guidelines and recommendations of the SAMS on biobanks. Names of participating patients and data generated as a result of this project will not be passed to unauthorized persons. Only Dr S. Fischer and Dr T. Silzle will have full access to the codes.

Biological material in this project is not identified by participant name but by a unique participant number. Biological material is appropriately stored in a restricted area only accessible to authorized personnel.

7.4 Retention and destruction of study data and biological material

The serum samples are stored for an indefinite period of time. Data of the project are archived for a minimum of 10 years after termination.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

Basic funding of the project will be provided by the "Forschungsfonds" of the Department of Medical Oncology and Hematology. Additional funding will be applied for by the "Forschungsförderung" of the Cantonal Hospital St. Gallen and additional potential sources as e.g. the "Schweizerische Krebsliga".

It is intended to present the results as an abstract on national and international congresses and to submit them as a research paper to a well-recognized haematological journal. All investigators will be informed in writing prior to any written communication or oral presentation about the project and invited to give comments.

9. References

Ordinance on Human Research with the Exception of Clinical trials (HRO) https://www.admin.ch/opc/en/classified-compilation/20121177/index.html

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   (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects)
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