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Immune response to COVID-19 vaccination in patients with autoimmune disorders on various types of immunosuppressive treatments

Submission date
16/03/2021

Recruitment status
No longer recruiting

Registration date
18/03/2021

Overall study status
Completed

Last Edited
17/01/2025

Condition category
Infections and Infestations

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
COVID-19 is a condition caused by the coronavirus (called SARS-CoV-2) that was first identified in late 2019. This virus can infect the respiratory (breathing) system. Some people do not have symptoms but can carry the virus and pass it on to others. People who have developed the condition may develop a fever and/or a continuous cough among other symptoms. This can develop into pneumonia. Pneumonia is a chest infection where the small air pockets of the lungs, called alveoli, fill with liquid and make it more difficult to breathe.
As the SARS-CoV-2 pandemic has spread throughout the planet, all hope is placed on the effect of vaccination. SARS-CoV-2 vaccination is not contraindicated (advised against) in patients with autoimmune disorders nor is it contraindicated in immunocompromised patients. The Czech Gastroenterological Association recommends SARS-CoV-2 vaccination in patients with inflammatory bowel disease (IBD). One of the major criteria of vaccination effectiveness in phase I and phase II clinical trials was the antibody response in healthy volunteers, but cellular immunity plays an important role as well. Two doses of the BNT162b1 vaccine result in a strong antibody response. Antibody levels in immunocompromised patients vaccinated against the influenza virus were increased less than in immunocompetent patients. It is not known how the immune response is modified after the SARS-CoV-2 vaccine in people with autoimmune disorders. This information will be very important in the near future.

Who can participate?
Patients over 18 years of age with clinically stable IBD or autoimmune hepatitis (AIH) who are scheduled for SARS-CoV-2 vaccination within a month may be included. Patients with IBD can be treated either without immunosuppressive therapy (e.g., 5-aminosalicylic acid only) or with azathioprine alone or with one of the anti-TNF alpha biologics alone or in combination with azathioprine. Patients with autoimmune hepatitis may be treated with a low-dose corticosteroid with or without azathioprine. Other treatment regimens cannot be included. In addition, healthy volunteers who are scheduled for SARS-CoV-2 vaccination within a month (Group E) may be included.

What does the study involve?
The study consists of a total of three visits in which the patients will fill out a questionnaire and a blood sample is collected for detection of antibodies against SARS-CoV-2, total immunoglobulin G levels, and various other immune system parameters. The first blood sample also includes an examination of complete blood count and basic biochemistry to determine the activity of IBD or AIH, and an examination of the level of 25-hydroxyvitamin D, which plays an important role in immune functions. The first visit and inclusion in the study must take place within 1 month before the start of SARS-CoV-2 vaccination, the second visit is scheduled 1 month after the end of vaccination and the third and last visit is scheduled 6 months after the end of vaccination. Vaccination against SARS-CoV-2 is voluntary and is carried out through the national vaccination program. Vaccination is not provided in the study.

What are the possible benefits and risks of participating?
Thanks to this study, participants will be able to find out for free how effective was the SARS-CoV-2 vaccination in terms of the production of antibodies and cellular immune response. The results will be available to them after consulting their attending gastroenterologist or hepatologist. At the same time, they will find out for free their level of 25-hydroxyvitamin D and whether they need substitution therapy.
The risks to the patient from this study are minimal. Obtaining three blood samples at the aforementioned intervals is not associated with the risk of long-term complications and every questionnaire takes a maximum of 5 minutes to complete. No non-standard drugs are administered and no procedures are performed during this study. Blood samples may be temporarily stored in case of analytic failure and then are discarded. No tests other than those intended for the study will be performed.

Where is the study run from?
Pilsen University Hospital (Czech Republic)

When is the study starting and how long is it expected to run for?
February 2021 to April 2022

Who is funding the study?
1. Ministry of Health (Czech Republic)
2. Charles University Research Fund (Czech Republic)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Protocol serial number
Nil known

Study information

Scientific Title
Humoral and cellular immune REsponse to SARS-CoV-2 vaccination in adult Patients with stable inflammatOry bowel disease or autoimmuNe hepatitis treated with different immunoSuppressive regimens: observational, prospectivE, controlled, single-center study

Acronym
RESPONSE

Study objectives
Main study hypotheses:
1. The immune response to SARS-CoV-2 vaccine is less pronounced in patients with idiopathic bowel diseases (IBD) and in autoimmune hepatitis (AIH) on immunosuppressive therapy than in patients without immunosuppressive therapy
2. The immune response to SARS-CoV-2 vaccine in healthy volunteers is comparable to the immune response in IBD and AIH patients without immunosuppressive therapy
3. There is no significant difference in the immune response to SARS-CoV-2 vaccine in patients on different immunosuppressive regimens (low dose corticosteroid, azathioprine, biologic therapy)
4. Total IgG level can be used to predict the subsequent post-vaccination antibody response in patients who have experienced and have not experienced SARS-CoV-2 infection in the past
5. History of SARS-CoV-2 infection adversely affects the immune response to SARS-CoV-2 vaccination

Side study hypotheses:
6. Patients with vitamin D deficiency (levels below 50 nmol/l, normal range 75-200 nmol/l) have a weaker immune response than patients without vitamin D deficiency
7. Previous influenza vaccination improves the immune response to SARS-CoV-2 vaccination

Ethics approval required

Old ethics approval format

Ethics approval(s)
Approved 04/03/2021, Local Ethical Committee at the Faculty Hospital in Pilsen (Edvarda Benese 13, 305 99, Pilsen, Czech Republic; +420 (0)377 423 275; snebergerova@fnplzen.cz), ref: 98/2021

Study design
Prospective observational single-center controlled study

Primary study design
Observational

Study type(s)
Prevention

Health condition(s) or problem(s) studied
Immune response to COVID-19 (SARS-CoV-2 infection) vaccination in patients on immunosuppressive therapy

Interventions
This study involves no intervention. The study team does not provide SARS-CoV-2 vaccination. The researchers only observe the immune response to SARS-CoV-2 vaccination. The vaccination itself is carried out through the national vaccination program. The SARS-CoV-2 vaccination is not performed at the study site. The researchers expect that the majority of patients will be vaccinated by their general practitioners. They bear no responsibility for the administration of the vaccine and any associated complications. Throughout the study, all necessary data concerning the SARS-CoV-2 vaccination are obtained from a survey.

The study consists of a total of three visits in which the patients will fill out a questionnaire and a blood sample is collected for detection of antibodies against SARS-CoV-2, total immunoglobulin G levels, and various other immunological parameters. The initial blood sample also includes an examination of complete blood count and basic biochemistry to determine the activity of IBD or AIH, and an examination of the level of 25-hydroxyvitamin D, which plays an important role in immune functions. The initial visit and inclusion in the study must take place within 1 month before the start of SARS-CoV-2 vaccination, the second visit is scheduled 1 month after the end of vaccination and the third and last visit is scheduled 6 months after the end of vaccination.

Intervention Type
Biological/Vaccine

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Not provided at time of registration

Primary outcome(s)
1. Demographic parameters measured using a questionnaire:
1.1. Age (Visit 1)
1.2. Sex (Visit 1)
1.3. BMI (Visit 1, 2, 3)

2. Evaluation of IBD (not in healthy controls):
2.2. Cohn's disease - disease form and location derived from medical record, disease activity assessed by Harvey Bradshaw index (Visit 1, 2, 3)
2.3. Ulcerative colitis – extent derived from medical record, disease activity assessed by Partial Mayo score (Visit 1, 2, 3)
2.3. Autoimmune hepatitis - activity derived from ALT level (remission defined as ALT no higher than 1.5 x ULN) (Visit 1, 2, 3)
3. Treatment of disease (Visit 1, 2, 3):
3.1 IBD groups A-C:
3.1.1. Mesalazine dose (g/d) derived from medical record
3.1.2. Azathioprine dose (mg/d) derived from medical record
3.1.3. Infliximab dose 5 mg/kg or 10 mg/kg, dosing interval, BT/vaccine interval for the first and second dose of the vaccine, derived from medical record
3.1.4. Adalimumab dose 40 mg/2 w or 80 mg/2 w, dosing interval, BT/vaccine interval for the first and second dose of the vaccine, derived from medical record
3.2. AIH group D (Visit 1, 2, 3):
3.2.1. Corticosteroid dose (mg/d) derived from medical record
3.2.2. Azathioprine dose (mg/d) derived from medical record
4. Laboratory parameters (group A-E):
4.1. Initial blood collection up to 1 month before the start of vaccination (Visit 1):
4.1.1. Complete blood count incl. white blood cell differential, assessed by standard hematologic measurement
4.1.2. Biochemistry: total bilirubin, AST, ALT, GGT, ALP, albumin, CRP, Fe; assessed by standard biochemistry measurement
4.1.3. Immunology and special tests: total IgG measured by nephelometry; SARS-CoV-2 IgG antibodies measured by ELISA; CD45, CD4, CD3, interferon-gamma, CD8, CD107, TNF-alpha, CD69, CD3, Ki67, CD137, CD27, CD45RO measured by flow cytometry
4.2. Blood collection 1 month after the second vaccination dose (Visit 2):
4.2.1. Total IgG measured by nephelometry; SARS-CoV-2 IgG antibodies measured by ELISA; CD45, CD4, CD3, interferon-gamma, CD8, CD107, TNF-alpha, CD69, CD3, Ki67, CD137, CD27, CD45RO measured by flow cytometry
4.2.2. ALT in Group D assessed by standard biochemistry measurement
4.3. Blood collection 6 months after the second vaccination dose (Visit 3):
4.3.1. Total IgG, SARS-CoV-2 IgG antibodies measured by ELISA
4.3.2. ALT in Group D assessed by standard biochemistry measurement
5. SARS-CoV-2 vaccination data:
5.1. History of SARS-CoV-2 infection before, during or up to 6 months after the vaccination (Visit 1, 2, 3) derived from questionnaires 2 and 3 respectively
5.1.1. Date of SARS-CoV-2 infection, severity of symptoms measured by scale in questionnaire at Visit 2
5.2. Adverse reaction to vaccination derived from questionnaire 2 and measured by scale in questionnaire at Visit 2

Key secondary outcome(s))
1. 25OH vitamin D measured by immunochemistry at Visit 1
2. History of previous influenza vaccination derived from questionnaire 1 at Visit 1

Completion date
01/04/2022

Eligibility

Key inclusion criteria
Group A: Patients with inflammatory bowel disease without immunosuppressant in maintenance therapy (50 patients)
Group B: Patients with inflammatory bowel disease on maintenance therapy with azathioprine (50 patients)
Group C: Patients with inflammatory bowel disease on biologic therapy (50 patients) (combination with azathioprine possible)
Group D: Patients with autoimmune hepatitis on low-dose corticosteroid maintenance therapy with or without azathioprine (50 patients)
Group E: Healthy volunteers (30)

Inclusion criteria common in all groups:
1. Interest in SARS-CoV-2 vaccination conducted by the national vaccination program (vaccination is not part of the study)
2. Signed informed consent
3. Age 18 years and above
4. No symptoms or positive test for SARS-CoV-2 infection in the last 2 months

Group-specific inclusion criteria:
Group A: Diagnosis of inflammatory bowel disease, no immunosuppressant in maintenance therapy
Group B: Diagnosis of inflammatory bowel disease, immunosuppressive therapy with azathioprine
Group C: Diagnosis of inflammatory bowel disease, biologic therapy with anti-TNF alpha (infliximab, adalimumab) with or without concomitant azathioprine
Group D: Diagnosis of autoimmune hepatitis, maintenance therapy with low-dose corticosteroid with or without azathioprine
Group E: No history of major chronic diseases, no chronic medication

Participant type(s)
Mixed

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
199

Key exclusion criteria
1. Contraindication to SARS-CoV-2 vaccination
2. Serious comorbidities (e.g. active oncological disease, terminal organ failure, severely limited

life expectancy)
3. Any other immunosuppressive or immunomodulatory treatment of comorbidities
4. Moderate or severe activity of IBD or autoimmune hepatitis/exacerbation of disease (Crohn's disease - Harvey-Bradshaw index > 5, ulcerative colitis - partial Mayo score > 4, autoimmune hepatitis – ALT activity > 1.5 x ULN)

Date of first enrolment
22/03/2021

Date of final enrolment
15/06/2021

Locations

Countries of recruitment
Czech Republic

Study participating centre
Pilsen University Hospital
Gastroenterology and Hepatology Section of 1st Department of Internal Medicine
Faculty of Medicine in Pilsen
Charles University Prague
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Pilsen
Czech Republic
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Sponsor information

Organisation
Charles University

ROR
https://ror.org/024d6js02

Funder(s)

Funder type
Government

Funder Name

Ministry of Health, Czech Republic - conceptual development of research organization (Faculty Hospital in Pilsen - FNPl, 00669806)

Funder Name
The Charles University Research Fund (project no.Q39)

Results and Publications

Individual participant data (IPD) sharing plan
The data that support the findings of this study will be available from the first author upon reasonable request. Informed consent for the anonymous publication of data will be obtained from all subjects. Personal data will not be shared.
Supporting data will be made available to Editorial Board Members and referees at the time of submission for the purposes of evaluating the manuscript and directly upon request to any reader on and after the publication date. Supporting datasets will be made available as Supplementary Information files that will be freely accessible on the journal's website upon publication.
The responsible investigator who should be contacted is Karel Balihar, MD, PhD (balihar@fnplzen.cz).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet			06/04/2021	No	Yes
Protocol file	in Czech	24/02/2021	06/09/2022	No	No