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Retrospective cohort of COVID-19 in patients with anti-CD20 treatment

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Abstract

Background: Anti-CD20 monoclonal antibodies are applied in a variety of autoimmune disorders and malignant diseases. Treatment with these agents causes a depletion in peripheral B-cells and loss of several B-cell functions, which typically last up to 9 – 12 months. Use of these monoclonal antibodies is associated with poor outcomes of COVID-19. With this study, we aim to study the risk and outcomes of prolonged COVID-19 in patients who had received anti-CD20 treatment prior to COVID-19.

Methods: All adult patients of Turku University Hospital, Turku, Finland, who were diagnosed with COVID-19 between 1.1.2020 and 1.9.2022 and who had received anti-CD20 monoclonal antibodies within 12 months prior to COVID-19 diagnosis were included in this retrospective study.

Results: 40 patients met the inclusion criteria. The patients median age was 64 years and 19 (47.5 %) were female gender. The median age was 64 years (interquartile range 55 – 75 years). 8 patients (20%) required intensive care and 10 (25%) died. 25 patients (64%) were admitted for COVID-19 within the first 14 days of symptoms, 12 (30%) were first admitted later within the first 30 days and 2 (5%) were first admitted for COVID-19 more than 30 days from onset of symptoms. A phenotype of prolonged pulmonary COVID-19, defined as respiratory symptoms, positive SARS-CoV-2 PCR, and interstitial pattern in high resolution computed tomography after 2 months from the onset of symptoms was observed in 7 patients (17.5%). Of those 7, 2 died due to COVID-19. In 2 cases of prolonged COVID-19, a short course of antiviral medication (remdesivir or ritonavir-boosted nirmatrelvir) in combination with antibody treatment directed against SARS-CoV-2 (tixagevimab-cilgavimab), resulted in prompt resolution of symptoms and clinical parameters.

Discussion: Anti-CD20 treatment is associated with a phenotype of prolonged COVID-19, suggestive for sustained viral replication. These patients may benefit from a combination of antiviral medication and monoclonal antibody therapy directed against SARS-CoV-2.

Introduction

Highly effective vaccines against COVID-19 provide good protection against severe COVID-19 for most of the population by inducing immunity through stimulation of T cells and antibodies directed at SARS-CoV-2 antigens [1,2]. However, certain patients remain at risk for severe disease despite repeated vaccinations, for instance due to age, comorbidities or immunosuppressive medications [3].

B cells play a key role in adaptive immunity by producing antigen specific antibodies, and lower B cell levels in plasma are associated with more severe outcomes in COVID-19 [4]. The majority of B cells express CD20 on their surface. Even though the biological function of CD20 remains unclear, in vivo studies have shown that CD20 is required for optimal T cell independent humoral immunity as well as T cell dependent immunity [5]. CD20 also play a role in B cell malignancies and certain immunological diseases [6]. Rituximab and obinutuzumab are monoclonal antibodies (mAb) which target the CD20 antigen on the surface of B cells. Anti-CD20 treatment is used as a treatment for several B cell mediated diseases such as haematological disorders and malignancies, rheumatoid arthritis, multiple sclerosis and vasculitis. Anti-CD20 mAb causes a depletion of B cells and may induce hypogammaglobulinemia for up to 12 months [7]. During this period, B cells are not capable of producing antibodies against newly encountered pathogens and efficacy of vaccination may be severely diminished. Therefore, patients receiving anti-CD20 mAbs may be at risk for severe COVID-19 despite vaccination [8]. Indeed, the concentration of antibodies against SARS-CoV-2 in patients' plasma who receive anti-CD20 mAbs is not sufficient and it causes more serious outcomes in COVID-19 [9].

During the Omicron wave in 2022, we observed in our clinic an apparent overrepresentation of relatively young patients with severe COVID-19 despite vaccinations, and with rituximab as a potential etiological agent, including several patients with prolonged disease and clinical features suggestive for ongoing viral replication. This retrospective cohort study was designed to explore the clinical picture of COVID-19 in patients with previous anti-CD20 mAb treatment and identify patients with possible prolonged viral pneumonia.

Methods

Patient population

All adult patients from Turku University Hospital, Turku, Finland, who were tested positive for SARS-CoV-2 PCR or who had a clinical diagnosis of COVID-19 (ICD-10 U07.1 – U010.9) between 1st of January 2020 and 31st of December 2022 and who had received anti-CD20 mAb treatment within 12 months before COVID-19 diagnosis were included in this study.

Clinical data

Patient information was collected from the electronic patient record system of the hospital.

Statistics

For this oberservational study, only describtive statistical methods are used, such as numbers, frequencies and percentages. REDCap was used for data collection and analysis. Data is reported according the PRISMA guidelines for observational studies.

Ethical statement

According to the Finnish Medical Research Act (488/1999, sections 1–3), non-interventional clinical studies do not require separate approval of the ethics committee. Approval for this study was obtained from the Turku University Hospital Clinical Research Centre (Turku CRC), approval number VSSHP/2022/26334. Informed consent was waved by CRC Turku (approval VSSHP/2022/26334). However, the patient presented as a case report provided informed consent. The research was conducted according to the principles of the World Medical Association Declaration of Helsinki.

Results

Most of the patients in our study were diagnosed with COVID-19 during the Omicron wave in 2022 and in our study all of the patients were vaccinated at least twice before the COVID-19 diagnosis. The first patient was admitted to hospital in August in 2021. Of 40 patients, 19 patients (47.5%) were female, and the median age was 64 years. 39 patients were tested positive with a reverse transcription polymerase chain reaction (RT-PCR) from a nasopharyngeal swab and 1 patient was tested positive at home with a rapid antigen test. All the patients had at least 2 vaccines against

SARS-CoV-2. 34 (85.0%) of the patients in our cohort were diagnosed with COVID-19 from the beginning of the Omicron era [10]. Baseline clinical characteristics are summarized in Table 1 and 2.

Thirty-nine of 40 patients (97.5%) were symptomatic when tested, 1 (2,5%) remained asymptomatic. In 39 cases (97.5%), the date of receiving rituximab could be determined, and in 1 case only the month could be determined retrospectively. Fifteen patients (37.5%) received anti-CD20 mAbs for lymphomas and 2 (5.0%) for chronic lymphocytic leukemia. Other indications for anti-CD20 mAb treatment were haematological disorders (n=5, 12.5%), rheumatic diseases (n=6, 15.0%), vasculitis (n=6, 15.0%), kidney diseases (n=1, 2.5%) and other connective tissue disorders (n=5, 12.5%). In most cases, anti-CD20 treatment was combined with other immunosuppressive drugs, as summarized in Table 3.

Five patients (12.5%) required intensive care and 10 (25%) died. Of those who died, 2 patients (20%) were female. The indications for anti-CD20 treatment of the patients who died, were systemic sclerosis (n=1 10.0%), pulmonary disease associated with granulomatosis with polyangiitis (n=1, 10.0%), chronic lymphocytic leukaemia of B cell type (n=1, 10%), autoimmune haemolytic anaemia (n=1, 10%), follicular lymphoma (n=1, 10%), mantle cell lymphoma (n=2, 20%), immune thrombocytopenic purpura (n=1, 10%), rheumatoid arthritis (n=1, 10%) and Sjögren's syndrome. Comorbidities among fatal cases included type 2 diabetes (n= 1, 10%), atherosclerotic heart disease (n=2, 20%), primary hypertension (n=6, 60%), asthma (n=1, 10%), chronic obstructive pulmonary disease (n=1, 10%) or interstitial pulmonary disease (n=3, 30%). The median age of the patients who died was 64 (range from 44 to 81 years). The median time from the onset of symptoms to death was 33 days (range from 13 to 161 days).

The study found several complications in addition to death which were portal vein thrombosis (1, 2.5%), opportunistic lung infections (4, 10%), kidney infarction (1, 2.5%), pulmonary embolism (3, 7.5%) and pneumomediastinum (1, 2.5%).

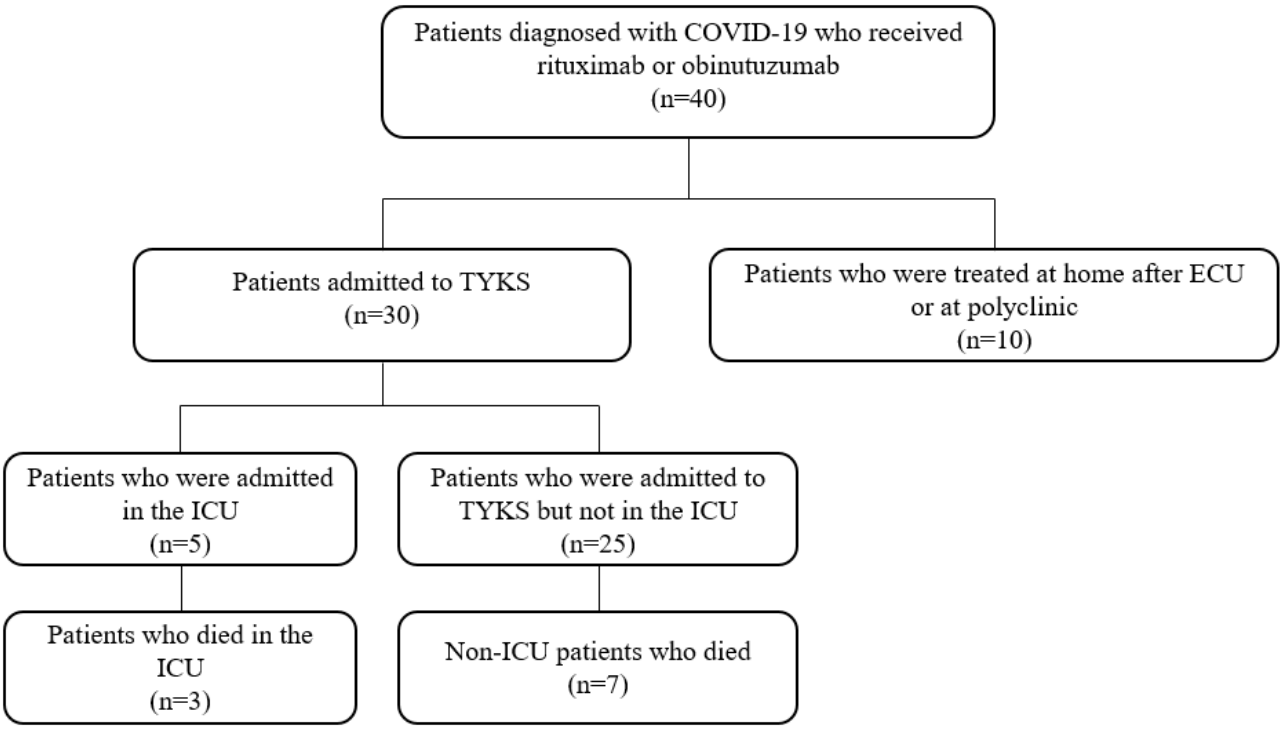

Figure 1. Flow chart. Abbreviations: TYKS, Turun yliopistollinen keskussairaala, Turku University Hospital; ECU, emergency care unit; ICU, intensive care unit

Prolonged viral pneumonia

To investigate whether anti-CD20 mAb treatment may predispose to prolonged viral pneumonia in COVID-19, we arbitrary defined prolonged viral pneumonia based on the following criteria:

- persistent or worsening clinical findings related to COVID-19 beyond from 60 days from infection, including:
    - Respiratory symptoms
    - AND radiologic features, such as ground glass infiltrate
    - AND/OR persistently positive SARS-CoV-2 PCR

We observed this clinical syndrome was observed in 7 patients (17.5%). The median age of these patients was 56 years. 6 had a finding of organizing viral pneumonia in high-resolution computed tomography (HRCT). All these 6 patients had a positive SARS-CoV-2 PCR after 2 months from the onset of symptoms. 3 of these patients had a bacterial or fungal infection as a complication diagnosed with bronchoalveolar lavation (BAL). Haemophilus influenzae, Prevotella melananinogenica and Aspergillus were diagnosed in 3 different cases. In those 7 patients the median duration of hospital admission was 14 days and from those patients 2 died due to COVID-

19 at day 134 and day 161 from start of symptoms. Clinical characteristics of this group are displayed in Table 2.

In 2 cases of prolonged COVID-19, a short course of antiviral medication (remdesivir or ritonavir-boosted nirmatrelvir) in combination with antibody treatment directed against SARS-CoV-2 (tixagevimab-cilgavimab) resulted in prompt resolution of symptoms and clinical parameters.

A case of prolonged viral pneumonia

A 47-year-old female was diagnosed with COVID-19 by PCR during the Omicron wave while BA.2 was the most common virus circulating in Finland. She had a medical history of seropositive rheumatoid arthritis, asthma, recurrent upper respiratory tract infections and recurrent otitis media. She had received her last dose of rituximab 115 days prior to COVID-19 diagnosis. In addition, she was on azathioprine and low maintenance dose prednisolone. SARS-CoV-2 PCR was positive on the first day of symptoms, with positive s-gene, suggestive of BA.2 variant, and a cycle threshold (Ct) of 20, while a second sample remained negative on day 24.

On the 30th day of symptoms, the patient visited the emergency care unit because of ongoing fever. Laboratory findings included a marked lymphocytopenia of 0.37 $x10^9$/L, CRP of 18 mg/L and human myxovirus resistance protein A (MxA) of >800 µg/L, in accordance with acute COVID-19. Chest X-ray showed hazy opacities in the right lung. The patient was admitted to hospital and intravenous antibiotic cefuroxime was started for possible bacterial pneumonia. The antibiotic was later changed to ertapenem, without apparent clinical benefit. On the 32nd day of symptoms, a CT of the lungs showed bilateral diffuse ground glass opacities matching with organizing pneumonia (OP). High dose prednisolone was started. By day 40 from the start of symptoms a bronchoalveolar lavation (BAL) was performed, which was positive only for Haemophilus antigen. Unfortunately, SARS-CoV-2 antigen was not tested from BAL. Haemophilus influenzae was also cultured from the sinus, as repeatedly previously. The patient was discharged after 7 days of hospitalization after her condition improved. On day 50 a patient call was made and she was still experiencing respiratory symptoms so a tetracycline antibiotic 500 mg x 3 for 10 days was prescribed for the Haemophilus influenzae found earlier in the bacterial culture.

On day 89, a CT was performed due to ongoing respiratory symptoms and showed bilaterally ground glass opacities in the peripheral regions of the lungs. On day 97 the patient was admitted again in TYKS because of ongoing respiratory symptoms, fever and shortness of breath during high dose of prednisolone 50 mg per day. By then, CRP was <1 mg/L, leukocytes 12.7 $x10^9$/L with 2% of lymphocytes, MxA was >800 µg/L and she had no detectable immunoglobulins

against COVID-19. SARS-CoV-2 PCR was repeated and was strongly positive with a cycle threshold (Ct) of 22. The sample was sent to the national institute for health and welfare (THL) for sequencing and Omicron BA.2 variant was diagnosed, while by then BA.4/BA.5 sublineages were dominating in circulation in Finland and BA.2 was only found in less than 5% of positive samples [11]. Because of clinical suspicion of prolonged viral pneumonia, prednisolone was rapidly decreased from 60mg/day to 10 mg/day. After a 3 day course of remdesivir (200 mg OD at day 1, followed by 100mg OD), she was treated with tixagevimab-cilgavimab 150 mg + 150 mg. By then, myxovirus protein A (MxA) was 490 µg/L, which fits to acute viral pneumonia [12]. Her symptoms quickly resolved and the SARS-CoV-2 PCR was negative on day 103 and the patient returned home.

Follow-up of SARS-CoV-2 PCR at day 110 was again positive and MxA had decreased to 60 µg/L and the patient was asymptomatic. The SARS-CoV-2 PCR turned negative at day 117 and MxA was <10 µg/L. The patient also reported relief of respiratory symptoms and she was able to gradually return to the maintenance dosage of prednisolone which was 5 mg per day. HRCT on day 172 revealed that the interstitial findings were completely resolved and the patient also remained asymptomatic.

Discussion

In our study, treatment with anti-CD20 is associated with high mortality and with a phenotype of prolonged pulmonary COVID-19 in a significant proportion of patients. The combination of prolonged symptoms, interstitial pattern in HRCT and persistent SARS-CoV-2 PCR positivity are suggestive of prolonged viral pneumonia with ongoing viral replication, especially in patients with anti-CD20 treatment as a possible aetiological factor through suppression of adaptive immunity and poor response to vaccination.

Antiviral treatment is mostly successful in the first week of COVID-19 [13]. However, prolonged viral replication in immunosuppressed patients provides a theoretical basis for antiviral treatment beyond the first phase of infection. Indeed, a combination of antiviral medication and monoclonal antibody therapy directed against SARS-CoV-2 resulted in prompt resolution of symptoms in several cases in our cohort. Other prolonged COVID-19 cases following the use of anti-CD20-depleting agents and potential benefit of monoclonal antibody treatment directed at SARS-CoV-2 have previously been reported by several others [14,15]. These studies had a sample of 1-22 patients. [14,16,17]. One study reported 22 patients with a prolonged or relapsed COVID-19 disease and 18 of them received full combination of 2 antivirals and mAbs and 4 of them received 2

antivirals only. 16 (73%) of the patients were asymptomatic and tested negative with nasopharyngeal PCR sample after 30 days from treatment [18].

As we describe in the case report, differentiation of prolonged viral pneumonia with ongoing viral replication may be difficult to differentiate from organizing pneumonia (OP) radiologically as well as clinically. OP may develop gradually as a subacute phase of lung tissue healing and is associated with granulation tissue buds within air sacs, composed primarily of myofibroblasts, fibroblasts, and a loose collagen-rich connective matrix. This condition can manifest as idiopathic, referred to as cryptogenic organizing pneumonia (COP), or as a result of various clinical factors like connective tissue disorders, medications, cancer, and infections such as COVID-19. Quick resolutions of symptoms and radiological findings upon start of corticosteroids has been describes by others [19]. However, our study suggests that some patients with OP may actually suffer from prolonged viral pneumonia with ongoing viral replication. The clinical manifestations should be considered in cases with poor response to corticosteroids.

It is important to recognize the difference between prolonged pulmonary COVID-19 and long covid. Prolonged pulmonary COVID-19 is related to immunosuppression, there is a specific aetiology involved as discussed above and it is important to be recognized and treated. Instead in long covid, dozens of symptoms and hundreds of biomedical findings have been reported. Long covid is believed to have multiple potential causes that may overlap. Various theories have been proposed to explain its development, including the presence of persistent SARS-CoV-2 parts in body tissues, immune system dysregulation with or without reactivation of underlying pathogens like Epstein-Barr virus (EBV) and human herpesvirus 6 (HHV-6), effects of SARS-CoV-2 on the microbiota and its viral population, autoimmune responses triggered by molecular mimicry, abnormal blood clotting and impaired endothelial function in small blood vessels [20].

Most of the patients in our cohort presented in the Omicron era of the COVID-19 pandemic. Before that, incidence rates remained low in Finland in comparison to most other countries. Therefore, nontherapeutic preventive measures may have successfully prevented them from exposure to SARS-CoV-2 until transmission peaked in 2022. During the first year of the COVID-19 pandemic, mortality due to COVID-19 was relatively low in Finland with 558 deaths (0.01% of general population), and the median age of the dead was 84 years [21]. In 2021 and 2022 the incidence of COVID-19 rose remarkably possibly due to newer variants and fewer restrictions. In 2021 952 people died because of COVID-19. [22]

In our cohort, 25% of these patients died. COVID-19 related mortality in these patients vary between from 1% to 32.7% in other retrospective studies [8,23,24]. The variation in mortality can be explained by the different sampling criteria. For instance, in our research, we only

analysed the outcomes of hospitalized patients but in other studies non-hospitalized patients with COVID-19 and anti-CD20 mAbs were also included. However, the studies have shown a high mortality of 25.0-34.2% in hospitalized patients as well [25,26,27].

Prolonged COVID-19 and high mortality in patients with anti-CD20 mAbs may be explained by poor antibody response to vaccines against SARS-CoV-2 [15,28]. The formation of antibodies against SARS-CoV-2 is decreased for up to 12 months after anti-CD20 treatment which may result to more severe outcomes of COVID-19 [29]. The patients' comorbidities and other immunosuppressive drugs used might have also been a reason for the poor outcomes of COVID-19.

Timing of vaccination before anti-CD20 treatment might be important. One retrospective study showed that nine months of rituximab-to-vaccination interval maximize the immunological benefits of COVID-19 vaccines while avoiding unnecessary delay in vaccination and rituximab treatment for patients with immune-mediated dermatologic diseases [30].

The strength of our study was the ability to provide a well-defined study design that allowed us to examine the relationship between exposure and outcome over time. The retrospective nature allowed us to analyse existing data.

Our study has several limitations. First, the retrospective design implies risk of bias. During the Omicron phase of the pandemic, with high transmission rates, the PCR testing was not anymore available to all COVID-19 cases, while home testing with rapid antigen tests was increasingly applied. Therefore, especially mild cases might have been be missed. Furthermore, clinical findings may not always be adequately registered. We did not include a control group, as confounding factors would probably severely affect the findings. Second, our study included only the patients from the province of South-West Finland, which is relatively healthy in comparison with people living in most other regions of Finland [31]. Third, ongoing viral replication is difficult to prove in the clinical situation. SARS-CoV-2 PCR positivity may also appear after infection due to non-viable viral antigens. Hence, radiological findings may be of different origin, such as organizing pneumonia, as discussed previously. However, the combination of a possible aetiological factor, such as anti-CD20 mAb treatment, in combination with ongoing symptoms and clinical findings fitting to ongoing viral pneumonia are highly suggestive, especially in case of quick resolution of symptoms after anti-viral and directed SARS-CoV-2 antibody treatment.

The case definition used for prolonged viral pneumonia in our study may not be optimal. The criteria should be reconsidered in an international workgroup to define optimal criteria for the clinical and research settings. Prospective interventional studies should be performed in order to test diagnostic and therapeutic approaches in patients with suspected prolonged viral pneumonia related to COVID-19. Furthermore, anti-CD20 mAb could also be associated with

prolonged viral pneumonia linked to other pathogens. We are not aware of any studies on other respiratory viral diseases such as influenza, RS-virus or rhinovirus, in patients treated with anti-CD20 mAbs. This could be addressed in studies with either a retrospective or a prospective study design.

In summary, while there is still much to be learned about the relationship between COVID-19 and anti-CD20 monoclonal antibodies, individuals receiving anti-CD20 treatment should take extra precautions to protect themselves from COVID-19 and should consult with their healthcare provider about their specific risk factors.

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Table 1. Baseline characteristics of patients without prolonged COVID-19. Abbreviations: BMI, body mass Index; DNR, do not resuscitate; CRP, C-reactive protein; ALAT, alanine aminotransferase; MxA, the human myxovirus protein 1; LD, lactate dehydrogenase; ESR, erythrocyte sedimentation rate

Baseline characteristics	**All patients (n=40)**	**Q1-Q3**
Female gender, n (%)	19 (47.5)	
Age (years)	64	55-75
BMI (kg/m^2), (n=39)	27.8	24.2-30.7
Smoking status, n (%)		
Non-smoker	25 (61.0)	
Ex-smoker	13 (32.5)	
Smoker	2 (4.9)	
DNR previously, n (%)	1 (2.4)	
Hemoglobin (g/l)	117	102-130
Leukocytes (x 10^9/L)	5.3	3.6-7.4
Lymphocytes (x 10^9/L), n=23	0.58	0.35-0.78
CRP (mg/L)	44	16-82
ALAT (U/L), (n=32)	22	16-36
Creatinine (µmol/L)	77	57-100
Interleukin-6 (ng/L), n=27	54.7	22.9-155
MxA >800 (µg/L), n (%)	22 (0.52)	
MxA (µg/L), n=7	630	400-736
Ferritine (µg/L), n=27	1335	468-1782
LD (U/L), n=29	309	240-414
D-dimer<0.2 (mg/L), n	5	
D-dimer (mg/L), n=25	0.7	0.4-1.55
Procalcitonin (µg/L), n=29	0.15	0.07-0.27
ESR (mm/h), n=28	49	36-84
Days from symptoms or positive test to hospital admission (n=38)	10	3-18
Days from last anti-CD20 dose to date of arrival in TYKS	108	45-208
Duration of hospitalization (days)	7	3-16
Time in ICU (days), n=5	10	2-18
Death, n (%)	10 (25.0)	

Table 2. Baseline characteristics of patients with prolonged COVID-19. Abbreviations: BMI, body mass Index; DNR, do not resuscitate; CRP, C-reactive protein; ALAT, alanine aminotransferase; MxA, the human myxovirus protein 1; LD, lactate dehydrogenase; ESR, erythrocyte sedimentation rate

Baseline characteristics	**Patients with prolonged Covid-19 (n=7)**	**Q1-Q3**
Female gender, n (%)	3 (42.9)	
Age (years)	56	47-75
BMI (kg/m^2), (n=39)	27.5	22.1-29.4
Smoking status, n (%)	-	
Non-smoker	4 (57.1)	
Ex-smoker	3 (42.9)	
Smoker	-	
DNR previously, n (%)	-	
Hemoglobin (g/l)	110	105-125
Leukocytes (x 10^9/L)	3.5	2.8-6.6
Lymphocytes (x 10^9/L), n=23	0.37	0.26-0.77
CRP (mg/L)	35	15-59
ALAT (U/L), (n=32)	35	17-59
Creatinine (µmol/L)	73	55-79
Interleukin-6 (ng/L), n=27	83.0	57.8-128
MxA >800 (µg/L), n (%)	5 (71.4)	
MxA (µg/L), n=7	660	
Ferritine (µg/L), n=27	1739	801-2370
LD (U/L), n=29	284	240-346
D-dimer<0.2 (mg/L), n		
D-dimer (mg/L), n=25	0.5	0.3-0.7
Procalcitonin (µg/L), n=29	0.07	0.05-0.13
ESR (mm/h), n=28	62	42-87
Days from symptoms or positive test to hospital admission (n=38)	20	16-33
Days from last anti-CD20 dose to date of arrival in TYKS	123	26-161
Duration of hospitalization (days)	14	3-43
Time in ICU (days), n=5	-	
Death, n (%)	2 (28.6)	

Table 3. Other immunomodulatory drugs and anti-CD20 indications

Other immunomodulatory or anti-inflammatory drugs used	**n**
Azathioprine	2
Bendamustine	4
Corticosteroids	15
Cyclosporine	1
Cyclophosphamide	3
Cytarabine	1
Doxorubicin	2
Etoposide	2
Hydroxychloroquine	3
Lipegfilgrastim	1
Methotrexate	5
Mycophenolate	4
IvIg (Nanogam)	1
Salazopyrin	1
Sulfasalazine	1
Venetoclax	2
Vincristine	3
Anti-CD20 indications	**n (%)**
Lymphoma	15 (37.5)
Chronic lymphocytic leukemia	2 (5.0)
Vasculitis	6 (15.0)
Autoimmune hemolytic anemia	4 (10.0)
Connective tissue disorders	10 (25.0)
Multiple sclerosis	1 (2.5)
Chronic nephritic syndrome with diffuse mesangiocapillary glomerulonephritis	1 (2.5)
Immune thrombocytopenic purpura	1 (2.5)

Table 4. Treatment and complications. Abbreviations: HFNC, high flow nasal cannula; NIV, non-invasive ventilation; IvIg, intravenous immunoglobulin

Treatment	**n (%)**
No respiratory support	19 (48.0)
Supplemental oxygen (<15 L/min)	11 (27.0)
HFNC or NIV	7 (18.0)
Mechanical ventilation	3 (8.0)
Corticosteroids	25 (62.5)
Anticoagulation	25 (62.5)
Tocilizumab	4 (10.0)
Antibiotics	27 (62.5)
Ritonavir-boosted nirmatrelvir	2 (5.0)
Remdesivir	11 (27.5)
IvIg	8 (20.0)
Baricitinib	1 (2.5)
Antifungals	3 (7.5)
Complications	**n (%)**
Thromboembolic events	3 (7.5)
Pneumomediastinum	1 (2.5)
Death	10 (25.0)