An overview of CD19 in COVID-19: Insights from Primary Immunodeficiencies and B cell depleting therapies

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Reports for Autoimmune Diseases and COVID-19 were collected by PS. Reports for primary immunodeficiency diseases were collected by AJ and GG. All the authors contributed to the writing of the manuscript.

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CONFLICT OF INTEREST STATEMENT

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ABSTRACT

The evolution of COVID-19 as a global pandemic and emerging evidence from cohorts of patients have provided an immense opportunity to understand biological processes pertinent to development of the disease. The immune system is central to the development of characteristic hyperinflammation. In an attempt to understand the role of humoral immunity in COVID-19, reports encompassing patients with primary immunodeficiency (PID)(13 patients) and on B cell depletion therapies(39 patients) who had concurrent COVID-19 were reviewed. In PIDs, patients with common variable immunodeficiency had worse outcomes than patients with agammaglobulinemia. Among the patients on B cell depletion therapy, heterogenous outcome was seen. As a group, patients with multiple sclerosis had better outcomes as compared to patients with systemic autoimmunity. Further, increasing reports of autoimmunity and autoinflammatory diseases occurring in temporal relation to COVID-19 is also evidence for the pathogenic role played by B cells. B cell depletion in the setting of COVID-19 may not be harmful in all patients and in fact may be protective in some scenarios. Identification of risk factors associated with a worse outcome in patients on B cell therapy could provide a rationale for individualised management.

KEYWORDS: *COVID-19, B-cell, Primary Immunodeficiency, rituximab, anti-CD20 therapy, autoimmunity, rheumatic diseases*

Introduction

The COVID-19 pandemic has resulted in an unprecedented crisis necessitating a deeper understanding of disease biology. The disease in a minority of patients is severe and characterized by the development of respiratory distress, heralded by elevated cytokines, and influx of neutrophils and macrophages, resulting in widespread inflammation. Older age and presence of comorbidities such as cardiovascular disease, chronic kidney disease, hypertension, diabetes mellitus, and malignancy have been identified as risk factors portending worse outcomes [1]. Conventionally, immunosuppressed patients are considered to be at high risk in case of infectious outbreaks and therefore initially, were also considered as a risk group for severe COVID-19. However, the plethora of literature that has emerged during the pandemic has given new insights, and many of them seem to challenge conventional wisdom. Drugs that suppress the immune system have been used successfully in the treatment of COVID-19 such as dexamethasone[2] .

The major sources of evidence on the role of immune deficiency in modulating disease pathophysiology in COVID-19 is gained from studying patients suffering from primary immunodeficiencies(PID), as well as patients on immunosuppressive medications. PIDs are rare entities resulting from mutations in key genes involved in the development, maturation and function of the immune system. Nevertheless, as they form naturally occurring gene knockouts, they provide a unique opportunity to study gene function and response to the environment including infections. Apart from this, pharmacological suppression of the immune components is widely used to treat several autoimmune diseases spanning specialities of rheumatology,

oncology and neurology. This has resulted in a unique pool of patients who could potentially improve our understanding of the effect of immunosuppression in pathogenesis of COVID-19.

In this commentary, we sought to re-examine the available literature assessing the outcome of patients suffering from PIDs as well as those receiving ongoing or prior B-cell targeted therapies and concurrent COVID-19 as diagnosed by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) or Computed Tomography (CT) of the lung. As of 1st August 2020, data on 13 patients with primary immunodeficiency and 39 patients on B cell depletion therapies are summarised in Table 1 and Table 2, respectively and are discussed in the initial half of the paper. In the light of these cases, we hypothesise the relevance of B cells in COVID-19 in the latter part of the paper.

Lessons from PID: No B cells better than dysfunctional B cells?

In PIDs, we could retrieve 6 case reports describing a total of 13 patients (9 males) with a median age of 41(8-59) years who had concurrent COVID-19. Patients with autosomal recessive agammaglobulinemia(ARA)(P4) and X-linked agammaglobulinemia (XLA)(P1,P2,P3) had milder disease as compared to those with common variable immunodeficiency (CVID)[3, 4]. This suggests that recovery from COVID-19 is possible without B cell help. Additionally, the Bruton tyrosine kinase (BTK) enzyme deficient in XLA is also required for the activation of macrophages, and IL-6 production in COVID-19, as suggested by the success of acalabrutinib in treating hyperinflammation in COVID-19[5]. A child with specific antibody deficiency (SAD)(P13) also had a mild disease[6]. Further, among those with CVID, lower CD19 was associated with better outcome [3]. The only patient who died (P5) in the PID group had the highest CD19 levels and the highest IgA levels amongst all. The three patients with the highest

CD19 (P5, P6, P9) were also the ones who received tocilizumab[3]. Two other single case reports (P10, P11) described severe disease in patients with CVID requiring ventilation [7, 8]. This could imply that immune dysregulation including dysfunctional B cells contributes to the severe inflammatory phenotype in CVID. This is exemplified by P12 with autoimmune lymphoproliferative syndrome (ALPS) in whom COVID-19 triggered production of new onset autoantibodies against red blood cells resulting in severe hemolytic anemia that responded to intravenous glucocorticoids[9].

Lessons from anti-CD20 therapy: Cautious use in systemic autoimmunity

This group included patients with autoimmune diseases (rheumatological, neurological, hematological, dermatological) and hematological malignancies. Both case series as well as single case reports have been included.

Rheumatological diseases

This group includes three cases with anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV)-granulomatous polyangiitis (GPA)[10–12], four cases each with scleroderma (SSc)[13, 14] and rheumatoid arthritis (RA)[15, 16] and one patient with systemic lupus erythematosus (SLE)[18]. Median age of the group was 54 (27-84) years.

All three patients with GPA (P14,P15,P16) had received rituximab in the preceding 1 month. A 52 year old lady who had received rituximab a day before onset of COVID-19 developed delayed worsening necessitating mechanical ventilation[10]. However, she recovered despite long-standing AAV and additional comorbidities (hypertension and overweight). A 27 year old lady with recent diagnosis of GPA had a favourable outcome after treatment with supplemental

oxygen and tocilizumab[11]. However, most intriguing was the case of P16, a 77 year old lady who had a mild illness and cleared the virus even in the absence of anti-SARS-CoV-2 IgGs[12] .

Avouac *et al.* reported three patients (P17, P18, P19) with scleroderma who had severe COVID-19[13]. Though all of them recovered, delayed clinical worsening was observed. However, it is noteworthy that P17 and P18 recovered despite the presence of adverse prognostic factors (higher age in both, hypertension in the first patient and chronic kidney disease and pulmonary embolism in the second patient). Patient 18 received tocilizumab. Mortality was reported by Favalli *et al* in P20, a 32 year old lady with scleroderma and lung involvement. She was ventilated and treated with tocilizumab but unfortunately did not survive [14].

Of the four patients with RA, P21 and P22 had favourable outcomes [15]. P21, a 54 year old lady required supplemental oxygen, but improved with tocilizumab despite multiple comorbidities[16]. Patients P23 and P24 died. Risk factors included age and presence of comorbidities[17]. Hospital course of P23, a 71 year old male was complicated by shock and renal failure.

Gartshteyn *et al.*[18] reported a case series of lupus patients with COVID-19. There was only one confirmed COVID-19 patient, P25 who was on rituximab. P25 had mild symptoms, necessitating only outpatient treatment and subsequently recovered.

Apart from the twelve patients described above, Fredi *et al.* reported four patients (P26-P29) who were on concurrent or previous rituximab in a series of 65 confirmed COVID-19 patients[19]. All four patients required hospitalisation but recovered. Data regarding comorbidities, lab parameters and need for ICU stay/ventilation were not available.

Dermatological Diseases

P30, a 43 year old man with mucous membrane pemphigoid received intravenous immunoglobulin (IVIG) and also recovered despite multiple comorbidities[20].

Neurological Diseases

This group consisted of 10 patients (P31-P40) with multiple sclerosis (MS)[21–24] and 1 patient, P41 with neuromyelitis optica with a median age of 49 (25-60) years[25]. No mortality was reported in any of these patients. Most had no comorbidities and had mild disease or were asymptomatic. Patients were treated with rituximab/ocrelizumab and most patients had total depletion of CD19 levels documented within the preceding 3 months. Despite this, 3 out of 4 patients in whom the serological assay was done tested positive for anti-SARS-CoV-2 IgG/IgM[21]. Creed *et al.* described P41, a 59-year-old lady with anti-aquaporin-4-positive neuromyelitis optica[25] who also had a mild COVID-19 disease. However, diagnosis of COVID-19 was preceded by one month of intermittent flu-like illness though it is unclear if this was an atypical presentation of COVID-19[25].

Hematological malignancies

While cancer patients were initially considered to be at high risk for COVID-19 based on initial reports, subsequent studies suggest that mortality may not be related to the malignancy or ongoing anti-cancer therapy. He *et al.*[26] reported the outcome in 128 hospitalised patients with hematological malignancies. All patients were screened for COVID-19 by CT of lung and if positive, further confirmed by RT-PCR. Thirteen out of 128 patients had COVID-19, out of which five died. However, none of the 18 patients with non-Hodgkin's lymphoma (NHL) had

COVID-19. As CT was the first step and RT-PCR was not done at all, it is possible that at least some of these patients had mild disease. Demography, comorbidities treatment details of these NHL patients or their lymphocyte subsets are not mentioned, though it can be assumed that NHL patients were treated with rituximab -based intensive chemotherapy regimen [26]. Aries *et al.*[27] described clinical outcomes in 35 patients with hematological malignancy of which eight patients(P42-P49) underwent rituximab-based chemotherapy regimen. With the exception of two patients (P42 and P46), all were receiving rituximab at the time of COVID-19 testing and contrary to expectation, the only patient who died (P42) was the one not on ongoing rituximab at the time of COVID-19. P50, a 26 year old male with mediastinal large B cell lymphoma had a mild disease, despite being on intensive chemotherapy with DAEPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab)[28]. In another study, Tepasse *et al.* has reported mortality in 2 male patients (P51, P52) in their 60s [29]. P51 had diffuse large B cell lymphoma whereas P52 had mantle cell lymphoma. Both the patients developed cytokine storm, delayed respiratory failure and died. Both patients also had high procalcitonin levels. Persisting SARS-Cov-2 viremia in these patients indicates lack of viral clearance [29].

Put together, emerging data shows that in most patients, B-cell depletion may not always be detrimental. A dichotomy in response is noted in patients with neurological disease as compared to rheumatological illness and PID. Recent study on MS patients from the French registry reinforces the observation that disease modifying therapies including B cell depletion are not associated with severe COVID-19[30]. Of 347 patients, 55 were on B-cell depletion therapy (rituximab-17, ocrelizumab-38). Disability, age and obesity were independently associated with worse outcomes [30]. Notably, severe COVID-19 was more frequent in those not on disease

modifying therapy as compared to those on treatment. Of the 12 patients who died, only one was on anti-CD20 therapy (rituximab) and this patient had discontinued rituximab 18 months prior to onset of COVID-19. Three patients on anti-CD20 therapy required ventilation [30].

In contrast, in rheumatological diseases and PIDs, multiple patients had a prolonged course of illness requiring ventilation. In this group, two patients with RA and one patient each with systemic sclerosis (SSc) and CVID died [3, 14, 17]. Fredi *et al.* has recently reported that the adverse outcome in patients with rheumatic diseases was related to age and other comorbidities rather than the underlying diagnosis or immunosuppression[19]. While mortality in RA patients is consistent with the study by Fredi *et al.*, worse outcomes in other patients in the rheumatology group and death of P5 with CVID cannot be explained by age, comorbidities or degree of immunosuppression alone. For instance, as a group, AAV patients had a more immunosuppressive regimen than those with SSc and had received rituximab closer to the diagnosis of COVID-19[10–12]. Whether severe COVID-19 disease is related to the more widespread immunological aberrations associated with systemic autoimmune disease/CVID or the predominant organ affected being the lung in these two conditions needs to be investigated upon. Considering the heterogeneous outcome and potential for severe disease, it is prudent to be cautious in the use of rituximab in these patients until data from large registries are available. It is difficult to compare the lymphoma group with the other patient groups, in the absence of data related to CD19 levels, details of comorbidities and course of disease including ventilatory requirement and treatment received. Nevertheless, it is surprising to note that patients with lymphoma survived despite being on intense immunosuppression with rituximab, cyclophosphamide, hydroxydaunomycin, oncovin and prednisone (R-CHOP) at the time of diagnosis [27].

Humoral immunity is believed to generate neutralising antibodies that help in resolution of infection and B cell depletion is a known risk factor for infection. In this background, how could one account for the mild disease seen in some patients on anti-CD20 therapy? There is increasing evidence that T cells and innate responses are major determinants of outcome in COVID-19[31–35]. Viral clearance may be possible in the absence of a robust humoral response [35]. For instance, P16, the 77 year old lady with AAV recovered in the absence of antibodies [11]. Lack of consistent response to convalescent plasma therapy also seems to question the role of B cells in recovery from COVID-19[36, 37]. Furthermore, even in the general population, only low titers of neutralising antibodies have been identified in those who recovered from COVID-19[38]. In this context, the presence of anti-SARS-Cov-2 antibody in some B cell depleted patients, though surprising, could be explained by the ability of anti-CD20 refractory tissue resident memory B cells to generate antibody responses[39]. If COVID-19 infection would produce long lasting immunity even in immunocompetent individuals is not known. However, it is indeed a matter of concern if those on B cell depleting therapy would be able to generate robust immunological memory in response to infection or vaccination (when it becomes available)[40].

The next question to be addressed is the biological plausibility of the beneficial effect of B cell depletion. This apparent paradox could potentially be explained by the following observations. Firstly, all antibodies generated against SARS-CoV-2 may not be protective. In fact, antibodies bound to activating Fc-receptor could result in a proinflammatory response and can be detrimental. This process is termed as antibody-dependent enhancement [41]. High titers of anti-SARS-CoV-2-specific antibodies found in those with severe disease could partly support this

theory [42]. Further, anti-spike IgGs in SARS-CoV/macaque models have been found to drive lung inflammation by recruiting and activating macrophages [43]. Secondly, unlike the typical cytokine release syndromes where the innate immune system is implicated, COVID-19 seems to have more of a subacute presentation and worsening is seen generally after one week of disease onset. The fact that this is also the time when humoral immunity comes into play could suggest a role for B cells in the dysregulated immune response [44]. B cell derived cytokines could also have an important role in the pathogenic inflammatory response. Thirdly, it has been found that Th2 cytokines increase with the severity of disease in COVID-19[45]. In this context, it is relevant to recall the close interactions between Th2 cytokines and B cells. Activated B cells can promote a selective Th2 response by modulating dendritic cells [46]. Finally, the occurrence of autoimmune and autoinflammatory diseases in temporal relation to COVID-19 is testament to the development of pathogenic autoantibodies and immune activation [47]. Immune thrombocytopenia, autoimmune hemolytic anemia, antiphospholipid antibodies and coagulopathy, Guillain-Barré syndrome and Kawasaki-like multisystem inflammatory disease have been described following COVID-19[47]. This is not unexpected as viral infection is known to trigger autoimmunity by mechanisms of molecular mimicry or bystander activation[48]. In one such instance of autoimmune hemolytic anemia following COVID-19, a 61 year old male patient was treated with rituximab following inadequate response to steroids [49].

In conclusion, the present observations suggest that B cells have a complex role in modulating the pathophysiology of COVID-19. Heterogenous outcome in systemic autoimmune diseases could result from complex interactions of the numerous risk factors. Immune dysregulation of the primary disease, therapeutic immunosuppression by rituximab and other drugs, age and other

comorbidities could all have a role in determining outcome in COVID-19. Identification of risk factors associated with a worse outcome in patients on B cell therapy could provide a rationale for individualised management. At the same time, it would be prudent not to defer therapy in patients at a high risk of relapse of their primary disease. Therefore, there is an unmet need for a systematic study to evaluate the effect of B-cell depletion in COVID-19. The other important aspect which has not escaped our attention is the potential for B- cell depletion as a therapeutic option at least in a subset of patients with hyperinflammatory response in COVID-19. As of date, while there are many immunosuppressants in clinical trials for COVID-19, anti-CD20 therapy is not yet one of them.

CONFLICT OF INTEREST STATEMENT

Authors declare no conflicts of interest.

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TABLES

Table 1 Summary of PID cases with COVID-19

XLA-X-linked agammaglobulinemia

ARA- autosomal recessive agammaglobulinemia

CVID-common variable immunodeficiency

SAD- specific antibody deficiency

ALPS-autoimmune lymphoproliferative syndrome

c/c- Chronic

COPD-Chronic obstructive pulmonary disease

HTN-Hypertension

ILD-Interstitial lung disease

ITP-Immune thrombocytopenia

IVIG-Intravenous immunoglobulin

HCQ-Hydroxychloroquine

MMF- Mycophenolate Mofetil

CXR-Chest X ray

GGO-Ground glass opacity

DAT- Direct antiglobulin test

B/l-Bilateral

BAL- Bronchoalveolar lavage

¶-CT of lung

§-Mechanical ventilation unless specified

+/- indicates patient was continuing hospitalisation

Table 2 Summary of patients on B cell therapy and COVID-19

AAV-anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis

GPA -granulomatous polyangiitis

SSc-Systemic sclerosis

RA-Rheumatoid arthritis

RRMS- Relapsing-remitting multiple sclerosis

PPMS-Primary progressive multiple sclerosis

SPMS-Secondary-Progressive Multiple Sclerosis

DLBCL-Diffuse large B cell lymphoma

FL-Follicular lymphoma

MCL-Mantle cell lymphoma

CYC -Cyclophosphamide

TNFi-TNF inhibitor

MMF- Mycophenolate Mofetil

MTX-Methotrexate

Lef-Leflunomide

Pred-Prednisolone

RTX-Rituximab

IFN β -1a interferon beta-1a

R-CHOP- Rituximab, Cyclophosphamide, Hydroxydaunomycin, Oncovin and Prednisone

DA-EPOCH-R- Dose-adjusted Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin, and Rituximab

R-DeVIC -Rituximab, Dexamethasone, Etoposide, Ifosfamide, Carboplatin

COPD-Chronic obstructive pulmonary disease

HTN-Hypertension

DM-Diabetes Mellitus

ILD-Interstitial lung disease

PAH-Pulmonary Arterial hypertension

CKD-Chronic Kidney Disease

BMI- Body Mass Index

B/l-Bilateral

CXR-Chest X ray

GGO-Ground glass opacity

¶ -CT of lung

§-Mechanical ventilation unless specified

+/- indicates patient was continuing hospitalisation

Patient Name	Age(yrs)/Sex	Primary Diagnosis	Age at diagnosis(in yrs unless specified)	Treatment for primary diagnosis	Comorbidities	Clinical features COVID 19	CRP in mg/l	Ferritin in µg/L	CD3 cell count in mm3	CD4 cell count in mm3	CD8 cell count in mm3	NK cell count in mm3	CD19 cell count in mm3 (Time between COVID-19 diagnosis and CD19 estimation)	IgG in mg/dl	IgA in mg/dl	IgM in mg/dl	Imaging	Other Complications	Oxygen requirement	Ventilation§ (Day of ventilation from onset of disease)	Treatment for COVID 19	Outcome	Days to recovery/death from onset of disease	Course of Hospital stay	Authors
P1	34/M	XLA	4 mo	IVIG	Nil	fever, cough	78	469	1040	495	509	11.6	0(0)	860	ND	ND	CXR-Interstitial pneumonia	nil	no	no	IVIG, HCQ, lopinavir/ritonavir	Recovered	22	admitted on d8, recovered on d 22	Soresina
P2	26/M	XLA	1	IVIG	Nil	vomiting, anorexia	3.6	774	1791	849	578	5.3	0(0)	863	ND	ND	CXR-Interstitial pneumonia	nil	no	no	IVIG, HCQ, azithromycin, ceftriaxone	Recovered	ND	ND	Soresina
P3	34/M	XLA	1	IVIG	Bronchiectasis	high fever	26	ND	1600	900	700	28	0(4)	800	0	0	CXR-mild interstitial alveolar infiltrates	nil	no	no	HCQ ceftriaxone, lopinavir/ritonavir	Recovered	14	Admitted on d6, recovered on d14	Quintil
P4	53/M	ARA	18	IVIG	Rt upper lobectomy for bronchiectasis, c/c sinusitis, COPD, Bronchiectasis	Asymptomatic	1	ND	1247	480	739	25	0(2mo)	750	0	0	↑similar to pre-covid	nil	no	no	HCQ, azithromycin, darunavir/cobicistat	Asymptomatic	0		Quintil
P5	59/F	CVID	48	IVIG	c/c sinusitis, c/c bronchitis	high fever, dyspnea	ND	ND	1030	672	338	46	400(2mo)	897	30	33	ND	ND	yes	yes	Tocilizumab, HCQ, azithromycin	Died	17	ND	Quintil
P6	32/F	CVID	14	Nil	Melanoma	high fever, cough, dyspnea	7.5	4000	1800	950	850	30	200(2mo)	500	0	153	↑Interstitial pneumonia	nil	yes	no	Tocilizumab(2), HCQ, darunavir/ritonavir	Recovered	17+	Admitted on d13, improved on d17	Quintil
P7	57/M	CVID	49	IVIG	Asthma, HTN, obesity	high fever, cough, dyspnea	1200	ND	3200	2767	1653	21	96(4mo)	550	40	44	CXR-interstitial pneumonia, alveolar consolidation	Candida on BAL	yes	yes(d9)	lopinavir/ritonavir, remdesivir methylprednisolone	Recovered	34	Admitted on d5, recovered on d35	Quintil
P8	52/M	CVID	24	IVIG	ITP, lymphoproliferation, ILD	high fever, dyspnea	ND	ND	750	274	258	85	55(3mo)	662	11	8	↑Interstitial pneumonia	nil	no	no	HCQ, azithromycin, lopinavir/ritonavir	Recovered	11	Admitted on d6, recovered on d11	Quintil
P9	41/M	CVID	14	IVIG	c/c sinusitis	high fever, cough, dyspnea	315	7200	1500	800	700	15	278(6mo)	700	10	30	↑Interstitial pneumonia	nil	yes	yes(d8)	Tocilizumab(1), HCQ, piperacillin/tazobactam, lopinavir/ritonavir, remdesivir	Recovered	13+	Admitted on d8, improved on d13	Quintil

P10	53/F	CVID	ND	IVIG	Breast CA(on tamoxifen), Sjogren's Syndrome	fever, cough,dyspnea	166	ND	ND	ND	ND	ND	ND	1710	0	33	¶Multifocal confluent GGO	nil	yes	yes(d7)	IVIG,HCQ	Recovered	14	Admitted on d7, recovered on d21	Fill L
P11	53/F	CVID	29	IVIG	Hypothyroidism , bronchiectasis, Sjogren's Syndrome	fever, chills, productive cough, dyspnea, vomiting, diarrhea.	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	¶¶Multifocal bilateral patchy & confluent GGO with interlobular septal thickening and microvascular dilatation	nil	yes	yes(d7)	IVIG,HCQ,ceftriaxone , doxycycline	Recovered	14	Admitted on d6, recovered on d14	Rana Aljaberi
P12	17/M	ALPS	ND	Eltrombopag ,MMF	Nil	fever, dyspnea, pallor,jaundice	ND	ND	Positive	0	0	ND	ND	Hypogammaglobulinemia			CXR:Prominent perihilar markings	Evans syndrome ,New onset warm DAT positive (IgG 3+, C3 1+	yes	no	IV glucocorticoids, Transfusion	Recovered	2	ND	Wahls ter
P13	8/M	SAD	1	IVIG	Multi-lobar bronchiectasis	rhinorrhea,increased productive cough	Elevated	ND	ND	ND	ND	ND	ND	N	N	N	CXR-worsening lung infiltrates		no	no	HCQ,meropenem, clindamycin	Recovered	7	ND	Ahanchian

Patient Number	Age (in yrs)/ Sex	Primary Diagnosis	Age at diagnosis (in yrs)	Treatment for primary diagnosis	Comorbidities	Clinical features COVID 19	CRP in mg/l	Ferritin in µg/L	Total duration of B cell depletion therapy	Timing of last anti-CD20 therapy prior to covid	Cell count in mm3 unless specified (Time between COVID-diagnosis and CD19 estimation)	IgG in mg/dl	Imaging	Complications	Oxygen requirement	Ventilating (Day of ventilation from onset of disease)	Treatment for COVID 19	Outcome	Days to recovery/ death from onset of disease	Author
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Rheumatology

P14	52/F	AAV-GPA	20	Glucocorticoids, CYC (total cumulated dose=41 gr), TNFi, MMF, MTX, Lef (prior), Pred15, RTX	overweight, HTN	fever, cough	ND	ND	6 mo(4*375mg/m2+1500 mg)	1 day	ND	ND	¶Interstitial pneumonia CXR-B/I	nil	yes	yes(d18)	HQ, lopinavir/ritonavir	Recovered	29	Gulpain
P15	27/F	AAV-GPA	27	Pred30, RTX, Septtran	Nil	Fever, cough, dyspnoea	100	1601	2mo(4*375 mg/m2)	1mo	ND	ND	¶multifocal opacities	nil	yes	no	Tocilizumab, HCQ, azithromycin	Recovered	19	Sharmen
P16	77/F	AAV-GPA	75	Pred5, MTX, RTX	Sjogren's Syndrome, dyslipidemia	Fever, dyspnoea, cough	20	ND	500 mg maintenance	1 mo	0	ND	¶B/I GGO	nil	no	no	ND	Recovered	27	Fallet
P17	71/M	SSc, diffuse Ant-RNA polymyositis 3	67	Pred5, MTX, RTX	HTN, Dyslipidemia, No ILD/PAH	Fever, cough, dyspnoea	ND	ND	30 mo(500 mg 6monthly)	3 mo	0	700	¶Interstitial pneumonia	nil	yes	NIV(d19)	Antibiotics, heparin	Recovered	26	Avouac
P18	84/F	SSc, limited	68	Pred5, RTX	CKD, Pulmonary embolism, No ILD/PAH	Fever, diarrhoea, cough	ND	ND	53 mo(500 mg 8monthly)	10mo	0	1290	¶Interstitial pneumonia	nil	yes(d15)	no	Tocilizumab, Antibiotics, heparin, anakinra, corticosteroids	Recovered	23+	Avouac
P19	44/f	SSc, limited Ant-RNApolymyositis 3+	42	Pred2.5, MTX, RTX	Overweight, No ILD/PAH	Fever, cough, sore throat, myalgia	ND	ND	31(1000 mg 8monthly)	5.5 mo	0	950	¶Interstitial pneumonia	nil	yes	NIV(d23)	Antibiotics, heparin	Recovered	48+	Avouac
P20	32/F	SSc	ND	RTX, HCQ	ILD	ND	ND	ND	ND	ND	ND	ND	¶Interstitial pneumonia	nil	yes	yes	Tocilizumab	Died	ND	Favalli

P21	54/F	RA	ND	Pred5, RTX, MTX 10	HTN, DM BMI> 40	Fever, Cough Dyspnea, Diarrhea Loss of smell and taste	ND	ND	ND	ND	ND	ND	CXR: B/l lower lung opacities	nil	yes	no	Tocilizumab, HCQ, azithromycin/ lopinavir-ritonavir	Recovered	Haberman 10 Jan
P22	50/F	RA	ND	RTX	ND	ND	ND	ND	48	ND	ND	ND	CXR: B/l diffuse interstitial pneumonia	nil	ND	ND	Lopinavir-ritonavir	Recovered	Conticlin 31
P23	71/M	RA	ND	RTX, MTX 5	Mild COPD	fever, cough, chest pain	ND	ND	60mg(2x10 00 mg within 14d every 6 mo)	2 weeks	ND	ND	CXR-B/l pneumonia	Renal failure, shock	yes	yes	piperacillin/tazobactam, meropenem, inotropic support, Dialysis	Died	Schulze-Koops 12
P24	80/F	RA	ND	Pred5, RTX, MTX 10	Mild HTN	fever, dry cough, fatigue, dizziness	ND	ND	ND(2x1000 mg within 14d every 6 mo)	ND	ND	ND	ND	nil	yes	yes	ND	Died	Schulze-Koops 17
P25	ND/F	SLE	ND	ND	ND	Fatigue, low-grade fevers, myalgia, mild cough	ND	ND	ND	ND	ND	ND	ND	nil	No	No	Antibiotics	Recovered	Gartshteyn Y
P26	ND	Rheumatic disease	ND	RTX	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Fredi M
P27	ND	Rheumatic disease	ND	RTX	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	Fredi M
P28	ND	Rheumatic disease	ND	RTX	ND	ND	ND	ND	ND	On	ND	ND	ND	ND	ND	ND	ND	All four hospitals	Fredi M
P29	ND	Rheumatic disease	ND	RTX	ND	ND	ND	ND	ND	ongoing/prior RTX, timing	ND	ND	ND	ND	ND	ND	ND	Recovered but	Fredi M
Dermatology																			
P30	43/M	Mucous membrane pemphigoid	ND	Pred, RTX, 43 MMF	DM, HTN, BP H	Fever, malaise ,dry cough, dyspnea	ND	ND	3 mo-RTX 4 weekly	2 mo	ND	ND	peripheral multilobular opacity, GGO	nil	yes	no	IVIg, HCQ, oseltamivir, lopinavir / ritonavir, meropenem, vancomycin	Recovered	Daneshpazhoo 7h
Neurology																			
P31	60/M	RRMS	ND	glatiramer acetate, natalizumab(prior RTX 50)	Nil	fever, cough, dyspnea	ND	ND	24 mo	ND	0(3mo)	ND	CXR-Left hemithorax infiltrates	nil	no	no	HCQ	Recovered	Mecallana 9V
P32	49/M	RRMS	ND	glatiramer acetate(prior docrelizumab 43 ab	Nil	fever, cough, dyspnea	49.5	ND	24 mo	2 mo	0(2mo)	ND	normal	nil	no	no	lopinavir/ritonavir	Recovered	Mecallana 10V

P33	45/M	RRMS		Interferon beta-1a (prior), ocrelizumab	Smoker	fever, cough, dyspnea	8.3	ND		33 mo	2 mo	0(0)				CXR-bilateral infiltrates	nil	no		HQ, lopinavir/ritonavir, azithromycin	Recovered	Meca-Lallana V
P34	25/F	RRMS		Interferon beta-1a (prior), fingolimod (prior), RTX	Nil	Asymptomatic	ND	ND		14 mo	1 mo	0 wnl			nil	ND	nil	no		nil	Asymptomatic	Meca-Lallana V
P35	52/M	RRMS		Glatiramer (prior), ocrelizumab	Nil	Asymptomatic	ND	ND		12 mo	ND	0 ND			nil	ND	nil	no		nil	Asymptomatic	Meca-Lallana V
P36	58/M	PPMS		IFN beta-1a, glatiramer, fingolimod (prior), Ocrelizumab	Asthma	fever, cough	63.1	ND		24 mo	7 mo	0(0)			nil	CXR-normal	nil	no		supportive therapy	Recovered	Novi
P37	33/F	RRMS		IFN beta-1a, RTX	ND	Fever, muscle soreness, headache, productive cough, mild dyspnea.	35.6	ND		5mo	1g -5 mo prior	0.3%(0)			nil	ND	nil	no		supportive therapy	Recovered	Devogel
P38	43/F	RRMS		RTX	ND	Fever, cough, gastrointestinal alterations	ND	ND		ND	ND	ND			nil	ND	ND	ND		ND	Recovered	Montero Escribano
P39	43/F	PPMS		Ocrelizumab	ND	Ageusia, Anosmia	ND	ND		ND	ND	ND			nil	ND	ND	ND		ND	Recovered	Montero Escribano
P40	55/F	SPMS		Ocrelizumab	ND	Fever, cough, dyspnea, pneumonia, fatigue, Anosmia	ND	ND		ND	ND	ND			nil	ND	ND	ND		ND	Recovered	Montero Escribano
P41	59/F	NMOSD		Azathioprine, RTX	ND	Fever, cough, malaise	ND	ND		84 mo	ND	0(0)				CXR-prominent bronchovascular markings	nil	no		supportive therapy	Recovered	Creed
Haematology																						
P42		FL		RTX, Bendamustine	ND	ND	ND	ND		ND	Not on treatment at time of COVID-19 diagnosis	ND				ND	ND	ND		ND	Died	Aries
P43		DLBCL		R-CHOP	ND	ND	ND	ND		ND	Ongoing	ND				ND	ND	ND		ND	Recovered	Aries
P44		DLBCL		R-CHOP	ND	ND	ND	ND		ND	Ongoing	ND				ND	ND	ND		ND	Recovered	Aries

P45			DLBCL			R-CHOP	ND			ND												Recovere d	ND		Aries
P46			FL			RTX maintenanc e (after R- CHOP)	ND			ND												Recovere d	ND		Aries
P47			DLBCL			R-CHOP	ND			ND												Recovere d	ND		Aries
P48			MCL			RTX maintenanc e	ND			ND												Recovere d	ND		Aries
P49			FL			RTX maintenanc e	ND			ND												Recovere d	ND		Aries
			Mediast inal large B cell lympho ma																						
P50	26/M		DLBCL, relapse			DA-EPOCH- 26R	Febrile neutropenia foli chemo			ND		6 weeks(2 cycles)	3 weeks	ND	ND	ND	Arbidol Hydrochloride, LianHuaQingWen capsule	no				Recovere d		21	Li
P51	65/M		DLBCL, relapse			R-DeVIC	HTN			300	5000	several months induction and on maintenanc e	2 weeks	low	yes	yes(14)	Piperacillin/Tazobactam	Died				Recovere d	ND	22	Tepass
P52	66/M		MCL			RTX maintenanc e,ibrutinib	CKD			130	20,000le		2 weeks	low	yes	yes(14)	Piperacillin/Tazobactam	Died						30	Tepass