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Treatment of chronic or relapsing COVID-19 in immunodeficiency

Li-An K Brown MRCP[1,2], Ed Moran PhD[3], Anna Goodman DPhil[4], Helen Baxendale PhD[5], William Bermingham MBBS[6], Matthew Buckland PhD[7,8], Iman AbdulKhaliq MBBS[9], Hannah Jarvis MBBS[10], Michael Hunter FRCP[11], Surendra Karanam FRCPath[12], Aisha Patel MBBS[2], Megan Jenkins MBBS[3], Alexander Robbins MBBS[13], Sujoy Khan FRCPath[14], Thomas Simpson MBBS[15], Stephen Jolles MD PhD[16], Jonathan Underwood PhD[17,18], Sinisa Savic PhD[19,20], Alex Richter MD[6,21], Adrian Shields PhD[6,21], Michael Brown PhD[2,22], David M Lowe PhD[1,10] *.

1. Institute of Immunity and Transplantation, University College London, London, UK
2. University College London Hospital NHS Foundation Trust, London, UK
3. North Bristol NHS Trust, Bristol, UK
4. Guy's and St Thomas' NHS Foundation Trust, London, UK
5. Royal Papworth Hospital NHS Foundation Trust, Cambridge UK
6. University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
7. Barts Health, London, UK
8. Institute of Child Health, University College London, Great Ormond Street Hospital, London, UK
9. Mid and South Essex NHS Foundation Trust, UK
10. Royal Free London NHS Foundation Trust, London, UK
11. Royal Victoria Hospital, Belfast, UK
12. Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK
13. Imperial College Healthcare NHS Trust, London, UK
14. Hull University Teaching Hospitals NHS Trust, Hull, UK
15. Lewisham and Greenwich NHS Trust, London, UK
16. University Hospital of Wales, Cardiff, UK
17. Department of Infectious Diseases, Cardiff and Vale University Health Board, Cardiff, UK
18. Division of Infection and Immunity, Cardiff University, Cardiff, UK
19. Leeds Teaching Hospitals NHS Trust, Leeds, UK
20. Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK
21. Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK
22. Clinical Research Dept, London School of Hygiene & Tropical Medicine, London, UK

* Corresponding author: Dr David Lowe
Institute of Immunity and Transplantation
University College London
Royal Free Campus
Pond Street
London
NW3 2QG

d.lowe@ucl.ac.uk
020 7794 0500

Abstract

Background: Patients with some types of immunodeficiency can suffer chronic or relapsing infection with SARS-CoV-2. This leads to morbidity and mortality, infection control challenges and the risk of evolution of novel viral variants. Optimal treatment for chronic COVID-19 is unknown.

Objective: To characterise a cohort of patients with chronic or relapsing COVID-19 disease and to record treatment response.

Methods: We conducted a UK physician survey to collect data on underlying diagnosis and demographics, clinical features and treatment response of immune deficient patients with chronic (at least 21 days) or relapsing (at least two episodes) of COVID-19.

Results: We identified 31 cases with a median age of 49 years. Underlying immune deficiency was characterised by antibody deficiency with absent or profoundly reduced peripheral B cells; prior anti-CD20 therapy and X-linked agammaglobulinemia were most common. Clinical features of COVID-19 were similar to the general population, but the median duration of symptomatic disease was 64 days (maximum 300 days) and individual patients experienced up to five episodes of illness. Remdesivir monotherapy (including when given for prolonged courses up to 20 days) was associated with sustained viral clearance in 7/23 (30.4%) clinical episodes whereas the combination of remdesivir with convalescent plasma or anti-SARS-CoV-2 monoclonal antibodies resulted in viral clearance in 13/14 (92.8%) episodes. Patients receiving no therapy did not clear SARS-CoV-2.

Conclusions: COVID-19 can present as a chronic or relapsing disease in patients with antibody deficiency. Remdesivir monotherapy is frequently associated with treatment failure, but the combination of remdesivir with antibody-based therapeutics holds promise.

Key words: COVID-19; SARS-CoV-2; immunodeficiency; therapeutic monoclonal; remdesivir

Clinical implications: COVID-19 can become chronic in patients with immunodeficiency and optimal treatment for this situation remains unknown. Here, we demonstrate that the combination of antivirals and antibody-based therapeutics is highly effective.

Capsule Summary: In immunodeficient patients with chronic or relapsing COVID-19 disease, we observed that the combination of antivirals and antibody-based therapeutics (monoclonal antibodies or convalescent plasma) was highly effective and superior to antivirals alone.

Abbreviations

SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
COVID-19	Coronavirus Disease 2019
CTAG	COVID-19 Therapeutics Advice & Support Group
PCR	Polymerase Chain Reaction
XLA	X-linked Agammaglobulinemia
CD	Cluster of Differentiation
Ig	Immunoglobulin
CVID	Common Variable Immunodeficiency
CT	Computed Tomography
CRP	C-Reactive Protein
IVIG	Intravenous immunoglobulin
IQR	Interquartile range
g	gram
L	litre
NHS	National Health Service
CP	Convalescent plasma

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Introduction

Antibody-deficient patients suffer chronic infection with certain viruses,[1,2] and SARS-CoV-2 infection can also become persistent or relapsing.[3-8] This risks chronic ill health, permanent lung disease, intra-host evolution of viral variants,[9] and social isolation. Optimal treatment is not yet established.

We conducted a UK physician survey collecting anonymised data on immunosuppressed adults with prolonged or relapsing COVID-19 (≥21 days' duration and/or ≥2 episodes of clinical illness). The survey was sent to all immunologists in the UK via a professional network, to infectious diseases and other specialists via the COVID-19 Therapeutics Advice & Support Group (CTAG) and to individual clinicians who were known to have managed patients in the target group. Data were only derived from information collected as part of routine clinical care and were provided in fully anonymised form.

Results and Discussion

31 responses were received (Table 1). The median duration of symptomatic disease was 62 days (maximum 300 days); the median time between first recorded and most recent positive SARS-CoV-2 PCR was 48 days (>200 days in 4 patients).

The median age was 49 years. 17/31 (54.8%) had a primary immunodeficiency causing hypogammaglobulinaemia, with a high frequency of X-linked agammaglobulinemia (XLA), and 14/31 (45.2%) had secondary immunodeficiency, mostly previous anti-CD20 treatment. Accordingly, patients demonstrated a striking absence of peripheral blood B cells with a median count of zero; the maximum B cell count recorded was 0.056 x 10^9/L with a maximum 3% of blood lymphocytes. In contrast, T cell counts were relatively well preserved (Table 1). Immunoglobulin G trough levels were within an acceptable range for those on replacement therapy prior to COVID-19 diagnosis but low in those not previously on treatment. IgA and IgM concentrations were generally very low or absent.

Patients with XLA had a confirmed genetic diagnosis or absent Bruton tyrosine kinase (Btk) expression and one patient had confirmed Wiskott-Aldrich syndrome. Other patients with primary immunodeficiencies, including those with CVID, did not have a genetic diagnosis. Causes of secondary antibody deficiency are listed in Table 1.

Only 13/31 patients (41.9%) had other co-morbidities. 30 out of the 31 patients (97%) had been hospitalised at least once due to clinical COVID-19 illness. Patients presented with typical symptoms of COVID-19: 30/31 (96.7%) had a cough and 27/31 (87.1%) had a fever. Chest imaging (chest x-ray and/or CT scan) was compatible with COVID-19 in 30/31 patients and not reported in one. Where measured, viraemia was relatively common (7/12, 58.3%). No patients had received a COVID-19 vaccine prior to presenting with infection. 3 patients (9.7%) had died at the time of the survey, one from an unrelated infection after clearing SARS-CoV-2. Among patients who had cleared the virus and were alive, 6 still had persistent symptoms but 14 had fully recovered; among those who had not cleared the virus and were alive (n=8), all had persistent symptoms.

We recorded virological outcome per patient according to the maximal antiviral treatment received (Figure 1A), defined as remdesivir or antibody-based therapy (convalescent plasma and SARS-CoV-2-specific monoclonal antibodies). Among 20 patients who cleared infection (median symptom duration 51.5 days): 13 received a combination of remdesivir plus antibody-based therapy (8 REGN-COV2, 5 convalescent plasma); 5 remdesivir monotherapy ≤10 days per course; 2 remdesivir monotherapy for > 10 days in a single course. Viral clearance was delayed in 3 cases treated with remdesivir monotherapy and 1 case treated with combination therapy. Among 11 patients who did not clear the infection (median symptom duration 70 days): 1 received combination therapy (remdesivir plus convalescent plasma); 6 remdesivir monotherapy ≤10 days; 1 remdesivir monotherapy for >10 days; 3 no antiviral treatment (p=0.006 by chi-square test for treatment difference between the groups). Via logistic regression controlling for age, sex and underlying diagnosis, the odds ratio of clearing infection with combination therapy versus remdesivir monotherapy was 23.1 (95% CI 1.3-424.9, p=0.035).

The patient who received combination therapy but failed to clear SARS-CoV-2 died after a monophasic illness lasting 23 days. The patient with delayed clearance received sequential therapy (remdesivir followed three weeks later by REGN-COV2), while other patients received the therapies contemporaneously.

We also analysed each of the 62 episodes of clinical COVID-19 illness (Figure 1B). We classified outcomes as unfavourable (persistent PCR positivity, clinical relapse, death) or viral clearance. Episodes with successful outcome are described above. Among 42 episodes with unfavourable outcome, 3 had no treatment details, 22 received no treatment, 15 remdesivir monotherapy ≤10 days, 1 remdesivir monotherapy for >10 days, and 1 combination therapy (as above); p<0.0001 by chi-square test for difference in outcome according to treatment received. Overall, 16/23 (69.6%) episodes treated with remdesivir monotherapy had an unfavourable outcome and 7/23 (30.4%) had viral clearance (delayed in three instances).

We also analysed clinical outcomes (overall clinical improvement, reduction in fever, reduction in serum C-reactive protein (CRP), reduction in oxygen requirement and discharge from hospital) per episode of illness (Supplementary Figure 1). Many untreated episodes demonstrated some spontaneous improvement with discharge from hospital. However, fever and CRP often did not improve significantly. In contrast, for the vast majority of episodes treated with remdesivir or combination therapy (and where outcome data were available), there was improvement in fever, CRP and oxygen requirement, regardless of sustained viral clearance.

Immunosuppressive and immunomodulatory therapeutic approaches were tried in some patients. The most commonly prescribed treatment was dexamethasone or other corticosteroids, in 25/62 episodes (40.3%). Other treatments given were tocilizumab (3 episodes), anakinra (4 episodes), and IVIG (2 episodes). One patient additionally received inhaled tissue plasminogen activator. 6/62 (9.7%) clinical episodes were treated with immunosuppressive or immunomodulatory treatments without antiviral treatments; none of these resulted in viral clearance.

Overall, our survey of 31 antibody-deficient patients with COVID-19 has demonstrated a high burden of morbidity among this population and has highlighted that combination therapy with antivirals and antibody-based therapeutics is associated with the highest rate of viral clearance.

Compared to the general hospitalised population with COVID-19, our cohort tended to be younger and have less comorbidity[10]. The underlying immunodeficiency was almost invariably characterised by antibody deficiency including a high frequency of patients with X-linked agammaglobulinemia or prior anti-CD20 treatment: there was a striking absence or profound reduction in peripheral blood B cells across this cohort. Some patients in the cohort may have broader immune compromise including impaired T cell function, while monocyte function may be impaired in XLA, but the composition of this cohort nevertheless implicates B cells and antibodies as key immunological components required to clear SARS-CoV-2 infection.

There are several case reports of COVID-19 outcomes amongst antibody-deficient patients who have not received any specific proven antiviral therapy. Some have died[7,11], but full recovery from mild illness[11,12] and even severe disease with intubation[13,14] has been reported in others.

In our surveyed patients, all untreated episodes had an unfavourable outcome of persistent PCR positivity and/or clinical relapse or death, although patients were only included in analysis if they had at least 21 days duration of symptoms and/or at least 2 episodes of clinical illness, which introduced a deliberate bias. Thus, while the published literature confirms that mild disease and spontaneous clearance of infection is a possible outcome in these groups of patients, chronic or relapsing disease[15] may well require specific therapy.

We found that a significantly higher proportion of patients had sustained clearance of SARS-CoV-2 after treatment with combination antiviral therapy (remdesivir plus antibody therapy, 13/14 (92.8%) achieved viral clearance) as compared to those treated with remdesivir alone (7/14 (50%) achieved viral clearance, often delayed), or with no specific treatment (0/3 achieved viral clearance).

Remdesivir monotherapy was given in 23 out of 62 clinical episodes in our surveyed patients and led to mixed outcomes; 16/23 episodes (69.6%) had an unfavourable outcome and 7/23 (30.4%) had viral clearance (delayed in three cases). However, remdesivir treatment generally led to an improvement in physiological parameters (fever, CRP and oxygen requirement) even if there was no viral clearance and/or a subsequent clinical relapse. Remdesivir may therefore have utility in unwell patients where there is no access to antibody-based therapies (although there may be a risk of selecting resistant viral sub-populations).

Failure to clear SARS-CoV-2 from antibody-deficient patients after remdesivir monotherapy has been reported in similar patients.[3,5,8,16-18] However, a good response to remdesivir in antibody deficiency has been documented in other cases.[11,19] Notably, remdesivir was often used outside of UK commissioning guidelines at the time in the patients in our cohort (i.e. beyond 10 days from symptom onset) and some were treated with prolonged courses up to 20 days' duration. As numbers were small, it is unclear whether this approach was more successful than 'standard' (as per clinical trials) courses up to 10 days' duration.

None of the patients included in our survey had received anti-SARS-CoV-2 antibody therapy alone. However, successful treatment with convalescent plasma alone has been described[4-7,19] including in 16 out of 17 B-cell depleted patients with chronic COVID-19,[16] 8 out of 14 treated patients with secondary immunodeficiency,[20] and two patients with CVID and severe COVID-19.[21,22] In contrast, monotherapy with convalescent plasma[19] or REGN-COV-2[8] was not successful in other cases.

Combination therapy with remdesivir and convalescent plasma or REGN-COV2 was generally a successful strategy in our surveyed patients. Successful outcomes with combination therapy have also been demonstrated in other similar patients[17-19,23,24] but this strategy failed in a patient with CVID who died at day 30 despite maximal therapy,[25] similar to a patient in our cohort.

In summary, in predominantly B cell and antibody-deficient patients with chronic or relapsing COVID-19, a significantly higher proportion of patients experienced sustained clearance of SARS-CoV-2 after treatment with remdesivir plus antibody therapy compared to remdesivir alone or no specific treatment. Currently, access to antibody-based treatments is challenging in many parts of the world, while access to any antiviral therapeutic is often restricted to those with early disease. Although appropriate for immunocompetent individuals, this approach does not address the needs of chronically infected patients. Indeed, many of the patients reported here were only treated as part of large, open-label trials where they could equally have been randomised to standard of care, or due to favourable decisions from pharmaceutical companies' compassionate use committees.

From both a clinical and public health perspective, we encourage improved access to treatment for these patients via protocols or studies with careful monitoring for outcome. Well conducted observational studies can provide vital data on rare patients such as these and may even be preferable to large, randomised controlled studies where recruitment would be challenging and use of placebos can present ethical issues.

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Figure Legend

Figure 1. A. Eventual virological outcome according to maximal treatment received in 31 antibody deficient patients with chronic or relapsing COVID-19. **B.** Outcome per episode of clinical illness (n=62 episodes) among the patient group. CP, convalescent plasma.

Table 1. Demographic and background data on 31 patients included in the survey.

Age (median [range])	49 [20 – 80] years
Sex (n, % male)	20, 64.5%
Diagnosis	
Common variable immunodeficiency (CVID)	5
X-linked agammaglobulinemia (XLA)	8
Other primary hypogammaglobulinemia	3
Secondary hypogammaglobulinemia[‡], previous anti-CD20 treatment	12
Secondary hypogammaglobulinemia[#], no previous anti-CD20 treatment	2
Unspecified	1
IgG concentration (g/L)	
Trough level for patients on immunoglobulin replacement prior to COVID-19 diagnosis (median [IQR]; n=19)	8.8 [6.7 – 12.3]
At presentation with COVID-19 for patients not previously on immunoglobulin replacement (median [IQR]; n=12)	4.3 [1.6 – 5.0]
IgA concentration (g/L, median [IQR]; n=27)	0 [0 – 0.57]
IgM concentration (g/L, median [IQR]; n=27)	0 [0 – 0.18]
B cell count ($x10^9$/L, median [IQR]; n=27)	0 [0 – 0.004]
CD4+ T cell count ($x10^9$/L, median [IQR]; n=26)	0.46 [0.23 – 0.85]
CD8+ T cell count ($x10^9$/L, median [IQR]; n=24)	0.35 [0.27 – 0.80]
Ethnicity (n, % white)	26, 83.9%
Other co-morbidity present ◊ (n, %)	13, 41.9%
Episodes of clinical illness with COVID-19	
Total	62
Range per patient	1 – 5
Mean per patient	2
Total median duration of illness per patient at the time of survey *	64 days

Viraemic at any time	
Yes	7
No	5
Not known	19
SARS-CoV-2 antibodies in serum during infection	
Positive	3 †
Negative	18
Not tested	9
On immunoglobulin replacement therapy at time of survey	
Yes	21
No – patient died	3
No – does not meet NHS England criteria	6
No – experienced significant side effects	1

◊ Diabetes mellitus, hypertension, ischaemic heart disease, other heart diseases (e.g. arrhythmia, valvular heart disease), asthma, chronic obstructive pulmonary disease, other chronic respiratory disease

* In some instances, details were not provided for all episodes of illness (for example, those managed in the community) and this figure is therefore likely to be an underestimate.

† All patients had received antibody-based therapies

‡ Follicular lymphoma (3), mantle cell lymphoma (2), other lymphoma (2), Waldenstrom's macroglobulinemia (2), chronic lymphocytic leukaemia (1), acute myeloid leukaemia with stem cell transplant (1), rheumatoid arthritis (1)

B-acute lymphocytic leukaemia with CAR-T therapy (1), renal transplant (1)

Ig, immunoglobulin. IQR, interquartile range. CD, cluster of differentiation. NHS, National Health Service.