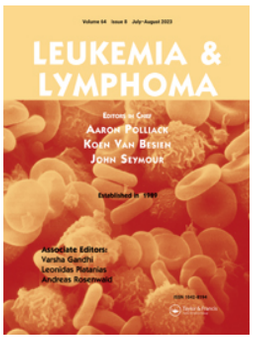

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LETTER TO THE EDITOR

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Improved COVID-19 outcomes in CAR-T patients in the age of vaccination and preemptive pharmacotherapeutics

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CD19-directed chimeric antigen receptor T-cell (CAR-T) patients are at high risk of severe SARS-CoV-2 infection and heightened mortality [1]. We previously reported COVID-19 outcomes for UK CAR-T patients prior to the availability of SARS-CoV-2-directed vaccination and pharmacotherapies. In our last analysis, 74% of patients developed severe disease and 86% died of COVID-19-related complications [2]. Since then, vaccinations, pharmacotherapies, and anti-inflammatory drugs (including corticosteroids) have reduced mortality in some patient groups, but data in CAR-T patients remains limited [3].

In December 2020, NHS England (NHSE) coordinated a UK-wide programme of SARS-CoV-2-vaccination, comprising three primary vaccines and seasonal boosters [4]. Full revaccination was recommended for all post-CAR-T patients from 3-months post-infusion due to B-cell aplasia [5].

Subsequently, in December 2021, NHSE launched the Covid Medicines Delivery Unit (CMDU) scheme (Figure 1) across the UK to provide SARS-CoV-2-directed pharmacotherapies (including nirmaltrevir-ritonavir, remdesivir, molnupiravir, sotrovimab) within 5–7 d of first positive test for symptomatic outpatients at high risk of severe COVID-19 to prevent hospitalization and death [4]. Drug selection was influenced by drug/infusion slot availability, potential drug interactions, co-morbidities, and patient preference.

Patients requiring hospitalization for COVID-19 were eligible for ≤10 d of IV Remdesivir regardless of symptom onset or need for supplemental oxygen, and in severe/critical cases anti-inflammatory drugs including corticosteroids and Tocilizumab could be used [4]. Patients with early hospital-onset COVID-19 could receive nirmatrelvir-ritonavir (first-line), remdesivir (second-line) or sotrovimab.

Here we review the impact of a national programme of vaccination and effective centralized delivery of preemptive SARS-CoV-2-pharmacotherapeutics on COVID-19 outcomes in adult CAR-T patients, comparing our current experience with our early pre-vaccination analysis [2].

This retrospective analysis (February 2021–May 2022) included patients from 7 UK centers diagnosed with COVID-19 infection following commercial or trial CAR-T products for large B-cell lymphoma, mantle cell lymphoma, or B-acute lymphoblastic leukemia. Data includes patient demographics, co-morbidities, and vaccination status at COVID-19 diagnosis. The diagnosis was confirmed by PCR or lateral flow test (LFT). Duration of infection was the interval between the first positive swab and the first of two negative swabs. Prolonged viral shedding was defined as >31 days based on the median duration observed in this cohort. Symptoms were graded by National Institute of Health (NIH) criteria as follows: (1) asymptomatic; (2) mild (without dyspnoea/abnormal chest imaging); (3) moderate (clinical/imaging evidence of lower respiratory disease and SpO_2 ≥94% on air); (4) severe (SpO_2 <94% on air; PaO_2/FiO_2 <300mm Hg/respiratory rate >30 breaths/min; >50% lung infiltrates), and (5) critical (respiratory failure, septic shock, and/or multiple organ dysfunction) [6]. We reviewed hospital/ICU admission rates, COVID-19-directed pharmacotherapies, and clinical outcomes according to all-cause mortality. Where available, absolute lymphocyte, neutrophil, and Immunoglobulin G (IgG) levels at presentation were recorded.

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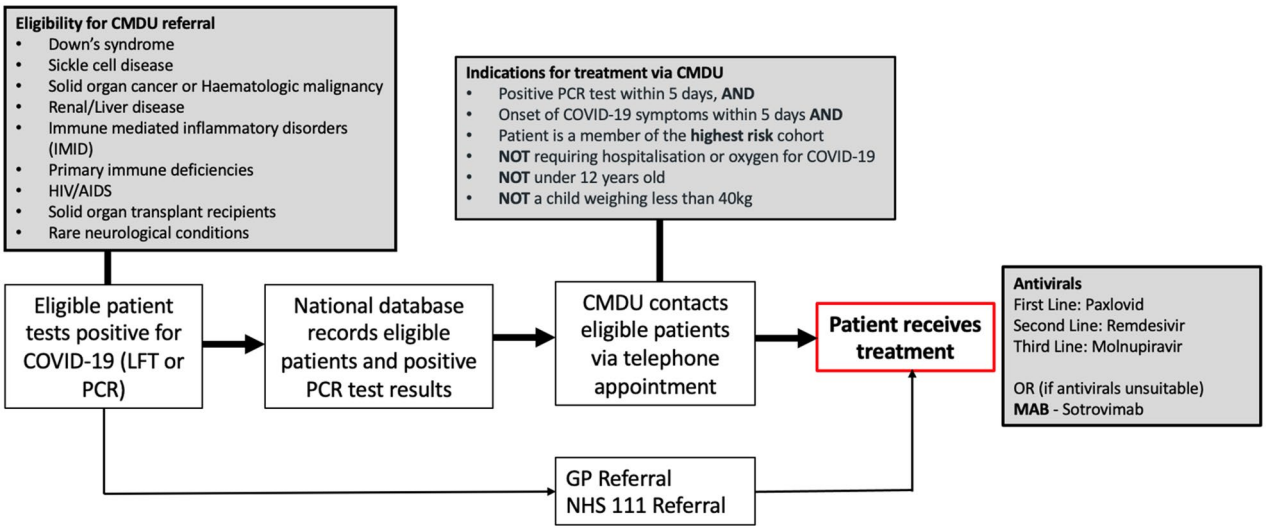

Figure 1. Flowchart displaying the CMDU pathway including the eligibility criteria for referral, indications for treatment and list of COVID-19 therapies available. (Adapted from NHS England CMDU referral pathway [4]). high-risk patients eligible for COVID-19 outpatient therapies are notified through their hospital specialist team *via* email or letter. Patients in this cohort who test positive for COVID-19 either through LFT or PCR are advised to register their results immediately on an online system matched to their national health records. This system would then prompt an automated electronic referral to the CMDU. Patients could also be referred through primary or secondary care providers. Following referral, patients were contacted by a CMDU clinician to assess eligibility for treatment and if so, were offered appropriate therapy. Triaging clinicians include doctors or allied health professionals such as nurse practitioners or pharmacists. CMDU: Covid medicines delivery unit; LFT: Lateral flow test; PCR: Polymerase chain reaction; MAB: monoclonal antibody.

Statistical analyses were mostly descriptive, but pre and post-vaccination cohorts were compared using logistic regression in STATA 16.1 (STATA-corp/Texas). $p < .05$ indicates significance.

SARS-CoV-2 infection was confirmed in 65 CAR-T patients. Median age was 60 years (range 21–78), 40/65 (62%) were male, 54/65 (87%) were Caucasian and 31/65 (48%) had co-morbidities. Patients had B-NHL (57/65; 88%) or B-ALL (8/65; 12%) and 56/65 (86%) were in remission at SARS-CoV-2 diagnosis. ECOG performance status was 0, 1, or 2 in 58% (37/64), 39% (25/64), and 3% (2/64) respectively. In this cohort, 64/65 (98%) of patients were vaccinated: 46/64 were vaccinated post-CAR-T, 14/64 were vaccinated pre-CAR-T, and the timing of vaccination was unknown in 4/64 patients. Data is illustrated in Table 1.

Patients were diagnosed with COVID-19 at a median of 9 months (range 0–43 months) post-CAR-T. 60/65 (92%) cases were community-acquired, with hospital-onset infection observed in 5/65 (8%). 60/65 patients (92%) were symptomatic, ranging from mild/moderate disease in 47/65 (72%) to severe/critical disease in 13/65 (20%). Hospital admission was required in 29/60 (48%) community-acquired COVID-19 cases including four patients with mild symptoms (Table S1). In total, 34 patients (29 community-acquired, 5 hospital-onset) were hospitalized for a median of 10 d ($n = 21$, range 2–91) and 8 patients ($n = 29$; 28%) remained in hospital at data cut-off. 4/65 (6%) patients required more than 1 hospital admission for ongoing/progressive COVID-19 symptoms.

Among the 34 hospitalized patients, 22 required oxygen support ($n = 31$, 71%). Nine patients required ICU admission ($n = 33$; 27%; all community-acquired) for a median of 4 d ($n = 5$; range, 3–5 d) where 4/9 (44%) required mechanical ventilation and 2/9 (22%) required inotropes.

Poor immune reconstitution was frequently observed at COVID-19 diagnosis (Table 1). Neutrophils $<1.0 \times 10^9$/L was observed in 11 patients ($n = 52$; 21%), with GCSF support in 22 cases ($n = 64$; 34%), and serum IgG was <4 g/L in 21 patients ($n = 35$; 60%), with 8 ($n = 64$; 13%) receiving immunoglobulins.

SARS-CoV-2-directed pharmacotherapy was administered in 48 patients ($n = 54$; 89%). 18/48 (38%) received outpatient treatment only. No treatment was administered in 6/54 (11%) patients, all of whom were asymptomatic or presented out of the CMDU treatment window.

Thirteen patients ($n = 61$; 21%) received single-agent antiviral therapies and 14 ($n = 62$; 23%) received single-agent MABs. Notably, eighteen patients were noted to have received consecutive or concurrent therapies with antivirals and MABs due to the severity or progression of symptoms necessitating inpatient management (Table S1). Corticosteroids were used in 13 patients ($n = 60$; 22%) and Tocilizumab in 4 patients ($n = 62$; 6%), all of whom had moderate/critical COVID-19, requiring oxygen support. Table S1 illustrates individual COVID-19 treatments received according to symptom severity.

We observed 9/65 (14%) patient deaths attributable to COVID-19 at a median of 43 d post-diagnosis ($n = 8$ range 16–105) and 10.5 months post-CAR-T infusion ($n = 8$; range, 2–30). Of the 9 deaths, moderate, severe, and critical COVID-19 symptoms were reported in 3/9 (33%), 1/9 (11%), and 5/9 (56%) cases respectively. One patient with asymptomatic COVID-19 died from progressive disease. Prolonged viral shedding was observed in 11 patients ($n = 22$; 50%), ongoing at a median of 50 days (range 32–127) from the initial COVID-19 diagnosis.

We looked at patient characteristics that could predispose to severe COVID disease namely age, sex, neutrophil

Table 1. Baseline demographics for $n = 65$ CAR-T patients with COVID-19.

Patient Characteristics, $N = 65$	N (%)
Age, median year (range)	60 (21–78)
Sex	
Male	40 (62)
Female	25 (39)
Ethnicity	
Caucasian	54 (87)
Asian	4 (7)
Others	4 (7)
Missing data	3
BMI	
≥18.5	1 (2)
18.5–24	30 (46)
≥25	23 (35)
≥30	11 (17)
Co-Morbidities	
None	34 (52)
Metabolic	19 (29)
Chronic Lung Disease (COPD, PE)	2 (3)
Others[b]	6 (9)
≥2 Co-Morbidities	4 (6)
Diagnosis	
B-NHL	57 (88)
B-ALL	8 (12)
Number of prior treatment lines	
2	42 (65)
3	12 (19)
≥4	11 (17)
CAR-T Cell Product	
Axi-Cel	38 (59)
Tisa-Cel	9 (14)
Brexu-Cel	4 (6)
Trial	14 (22)
Disease status at time of COVID-19 diagnosis	
CR	52 (80)
PR	4 (6)
SD	2 (3)
PD	7 (11)
Vaccinated (≥1 dose)	
Yes	63 (98)
No	1 (2)
Missing data	1
ECOG at time of COVID-19 diagnosis	
0	37 (58)
1	25 (39)
2	2 (3)
Missing data	1
Time from CAR-T to COVID-19 diagnosis, Months	
≤3 months	19 (29)
4–6 months	7 (11)
>6 months	39 (60)
SARS-CoV-2 Variant	
Delta	4 (21)
Omicron	15 (79)
Missing data	46
Symptoms	
Yes	60 (92)
Fever	*32/55 (58)*
Cough	*45/57 (79)*
Dyspnoea	*23/57 (40)*
Anosmia	*7/45 (16)*
Fatigue	*29/55 (53)*
Myalgia	*8/51 (16)*
Gastrointestinal symptoms	*9/51 (18)*
No	5 (8)
Missing data	1
NIH COVID Symptoms grade	
Asymptomatic	5 (8)
Mild	30 (46)
Moderate	15 (23)
Severe	6 (9)
Critical	7 (11)
Hospital admission	
No	31 (48)
Yes	29 (45)
Hospital-onset infection	5 (8)
Duration, median days (range), $n = 21$	10 (2-91)
Not discharged at time of data cutoff	8
Missing data	5
ICU Admission ($N = 34$ hospitalized patients)	
No	24 (73)
Yes	9 (27)
Missing data	1
Duration, median days (range), $n = 5$	4 (3-5)
Not discharged at time of data cutoff	1
Missing data	3
Oxygen support ($N = 34$ hospitalized patients)	
No support	9 (29)
Nasal cannula	11 (35)
High flow nasal cannula	4 (13)
Non-Invasive Ventilation	3 (10)
Intubation	4 (13)
Missing data	3
Requiring Inotropes, ($N = 34$ hospitalized patients)	
Yes	2 (7)
No	27 (8)
Missing data	5
Laboratory Values, N, median (range)	
ANC ($\times 10^9$/L), $n = 52$	2.09 (0.03 – 14.30)
ALC ($\times 10^9$/L), $n = 52$	0.42 (0.04-5.9)
IgG (g/L), $n = 35$	3.03 (0.8 – 12.99)
Requiring GCSF at time of COVID-19 diagnosis	
Yes	22 (34)
No	42 (66)
Missing data	1
Requiring IVIG at time of COVID-19 diagnosis	
Yes	8 (13)
No	56 (88)
Missing data	1
COVID-19 Therapies	
Yes	48 (89)
Single agent MAB	*14/62 (23)*
Single agent antivirals	*13/61 (21)*
Steroids	*13/60 (22)*
Tocilizumab	*4/62 (6)*
Convalescent plasma	*0/61*
Other trial drugs: Empagliflozin	*1*
No	6 (11)
Missing data	11
COVID-19 Outcomes	
Death due to COVID-19	9 (14)
Median time to death, days (range), $n = 8$	43 (16-105)
Prolonged viral shedding, $n = 22$	11 (50)
Median duration of viral shedding, days (range)	50 (32-127)

B-NHL: B-Non-Hodgkin's Lymphoma; B-ALL: B-Acute lymphoblastic lymphoma.

[a]Metabolic Co-morbidities - Hypertension, Diabetes, Obesity, Hyperlipidemia.

[b]Cardiovascular disease, chronic kidney disease.

count, time from CAR-T infusion to COVID infection, and timing of vaccination (whether they were vaccinated pre- or post-CAR-T infusion) and found no significant risk factors. When we performed this analysis on death from Covid alone, older age showed a significant association, with a more than doubling in the risk for each 10-year increase (OR: 2.55 (1.06–6.17), $p = .037$). When comparing this post-vaccination cohort with our published pre-vaccination cohort (January 2020–January 2021) [2], we observed *a* ~90% reduction in risk of severe COVID-19 (OPR: 0.12 (95% CI:0.04–0.38), $p < .001$), significant even when adjusted for patient age and time from CAR-T infusion (OR: 0.08 (95% CI:0.01–0.48), $p = .006$). We also observed a reduction in COVID-19-related death (13.9% vs 63.2%; OR: 0.09 (0.03–0.30), $p < .001$) or 0.05 (0.01–0.25), $p < .001$ adjusted).

To determine whether widespread availability of testing in the vaccinated cohort was contributing, we compared severe disease and death in the symptomatic vaccinated cohort with the pre-vaccination cohort and the conclusions were unchanged (severe disease: 27.6% vs 87.5%, adjusted OR: 0.05 (0.01–0.27), $p < .001$; covid deaths, 15.5% vs 75.0%; adjusted OR 0.06 (0.02–0.23), $p < .001$).

To summarize, SARS-CoV-2 infection can lead to severe disease and increased mortality in CAR-T patients [1,2]. We observed that vaccination and preemptive SARS-CoV-2-directed pharmacotherapies through the CMDU scheme was associated with a reduction in severe disease and mortality in CAR-T patients compared to our previous analysis of an unvaccinated patient cohort [2].

Vaccination in immunocompromised patients has been shown to reduce the incidence of severe COVID-19/mortality despite weak/absent serological responses [7]. Currently, most patients are fully vaccinated pre-CAR-T referral and routinely commence revaccination at 3 months post-CAR-T [5]. This belt-and-braces vaccination strategy may be contributing to better outcomes.

Novel pharmacotherapies can reduce severe/critical COVID-19, hospitalization, and death [3]. The centralized CMDU model described here permits community delivery of COVID-19-directed pharmacotherapies across the UK to patients with non-moderate/severe COVID-19 and has led to reduced hospital admission rates [8]. Immunomodulators remain important therapeutic options in hospitalized patients with moderate/critical COVID-19 requiring oxygen [9,10]. Combined therapy in immunocompromised patients is not routinely NHSE-recommended [4] and data is sparse and conflicting. Whilst some case reports indicate that combined antiviral/MAB treatment improves outcomes through reduced viral load/enhanced viral clearance [11,12], other studies show no difference in outcomes [13]. Prospective studies are needed, but for now combined therapy treatment decisions should be made by a multidisciplinary team.

Prolonged SARS-CoV-2 shedding continues to be a problem in CAR-T patients, leading to treatment delays, prolonged self-isolation, risk of SARS-CoV-2-flare, and chronic lung inflammation [14].

It was not possible to test the impact of different SARS-CoV-2 variants in this analysis, but the emergence of the Omicron variant in November 2021 has likely contributed to better outcomes here, as shown in other immunocompromised patient datasets [15].

This study has several limitations, being unpowered to definitively assess specific COVID-19 risk factors, and we were unable to directly compare pharmacotherapies due to treatment heterogeneity and the possible impact of viral variants. Further, multivariable analyses were not feasible due to missing data and low rates of severe disease. However, despite these limitations, the large reduction in risk of severe/critical COVID-19 for vaccinated vs unvaccinated patients [2] remained.

The combination of vaccination, centralized access to novel/preemptive therapies and the emergence of less virulent SARS-CoV-2 variants is likely associated with the lower risk of severe disease/mortality in CAR-T patients reported here. Nonetheless, despite advances, COVID-19 mortality remains high (14%), and future research toward more effective vaccines and (combined) pharmacotherapies will be key to improving outcomes.

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