full dose anti-coagulation for inpatients, or anti-platelet agents if not admitted to hospital.

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Competing interests

There are no competing interests.

Roshan Ramasamy[1]
Kate Milne[2]
Deanne Bell[3]
Simon Stoneham[4]
Timothy Chevassut[2,5]

[1]Intensive Care Department, Brighton and Sussex University Hospitals NHS Trust, Brighton, [2]Haematology Department, Brighton and Sussex University Hospitals NHS Trust, Brighton, [3]Department of Medicine, Brighton & Sussex University Hospitals NHS Trust, Brighton, [4]Department of Microbiology and Infection, Brighton and Sussex University Hospitals NHS Trust, Brighton and [5]Clinical and Experimental Medicine, Brighton and Sussex Medical School, Brighton, UK.
E-mail: roshan.ramasamy@gmail.com

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Interleukin-1 blockade with anakinra in acute leukaemia patients with severe COVID-19 pneumonia appears safe and may result in clinical improvement

As of 17 May 2020 the number of patients infected by coronavirus disease 2019 (COVID-19) worldwide has exceeded 4·5 million.[1] A subgroup of patients with COVID-19 pneumonia develop a hyperinflammatory syndrome which has a similar cytokine release profile to secondary haemophagocytic lymphohistiocytosis (HLH).[2] Immunomodulatory drugs are hypothesised to abrogate the dysfunctional immune response in hyperinflammatory COVID-19 and are currently being

investigated in clinical trials. Interleukin-1 (IL-1) blockage with anakinra has been shown to be safe and is associated with clinical improvement in patients with hyper-inflammatory COVID-19.[3]

Preliminary reports suggest that patients with an underlying malignancy have inferior outcomes from COVID-19.[4,5] Many haematology patients with COVID-19 will not be able to access novel immunomodulatory agents through clinical trials due to threshold laboratory values or recent use of other biologic agents. Therefore, off-label use of accessible therapeutic agents that have demonstrated benefit should be considered in haematology patients with concomitant COVID-19. In this report we demonstrate that anakinra is safe in haematology patients and resulted in a clinical improvement in three patients with acute leukaemia and confirmed or suspected COVID-19 pneumonia with a life-threatening hyper-inflammatory syndrome.

Patient one

A 40-year-old male patient with newly diagnosed acute myeloid leukaemia (AML) was commenced on induction chemoimmunotherapy (daunorubicin 50 mg/m^2, cytarabine 100 mg/m^2, gemtuzumab ozogamicin 3 mg/m^2) (Table I). On day 12, after starting treatment he became pyrexial and empirical antibiotics and antifungal agents were started. High-resolution computed tomography (HRCT) scan of the chest demonstrated ground glass opacities in the right upper lobe (Fig 1A). A combined nose and throat swab for SARS-CoV-2 was negative but a diagnosis of presumed COVID-19

Table I. Baseline patient characteristics and length of stay.

Patient No.	Sex	Ethnicity	Age	Haematological malignancy	Systemic anticancer treatment	Comorbidities	Symptoms	No. of days post anakinra until ITU discharge	Total length of stay
1	Male	Caucasian	40	AML	Cycle 1 DA* and gemtuzumab	Nil	Cough, rhinorrhoea, sore throat, diarrhoea, fever, rash	3	37
2	Male	Caucasian	31	AML	Cycle 1 DA* and gemtuzumab	Nil	Cough, rash, fever, dyspnoea, diarrhoea	7	43
3	Male	Caucasian	36	ALL	Cycle 2 of blinatumomab	Previous seizures	Fevers	N/A	30

*Daunorubicin and cytarabine.

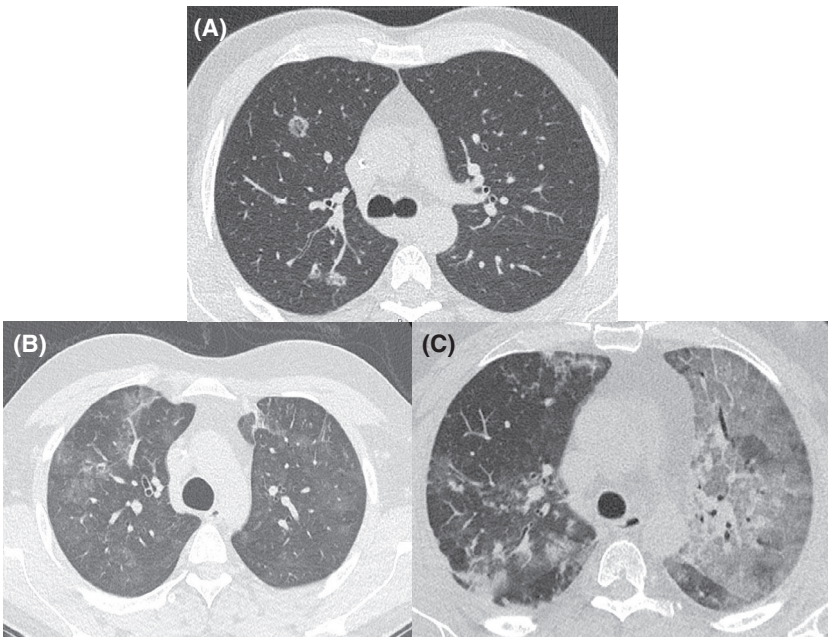

Fig 1. (A) Patient 1 – Axial view, high resolution computed tomography (HRCT) demonstrating three foci of parenchymal ground glass change surrounded by consolidation (the 'reverse halo' sign) in the right upper lobe. (B) Patient 2 – Axial view, chest HRCT demonstrating bilateral, multifocal ground glass change. (C) Patient 3 – Axial view, HRCT demonstrating widespread ground glass change most pronounced in the left upper lobe, predominantly subpleural and peribronchovascular consolidation and some interlobular septal thickening.

was made based on the typical appearances on imaging and the absence of another identifiable cause. Due to increasing oxygen requirements, the patient was transferred to the intensive care unit (ICU). A diagnosis of haemophagocytic lymphohistiocytosis (HLH) was considered after ferritin levels of 55 043 μg/l were noted along with persistent pyrexia, refractory thrombocytopenia (5×10^9/l), raised triglycerides (5·7 mmol/l) and a coagulopathy [International Normalized Ratio (INR) 2.4]. The H Score, which has a specificity of 86% for scores above 163, was calculated as 195. He was started on subcutaneous anakinra at a dose of 100 mg three times a day (TDS), dexamethasone and intravenous immunoglobulin (IVIg). The following day his oxygen requirements reduced and he defervesced. The anakinra and corticosteroids were weaned, the serum ferritin level fell, and the patient was discharged 35 days after commencing chemotherapy.

Patient two

A 31-year-old male, newly diagnosed with AML, was admitted for induction therapy (daunorubicin 50 mg/m^2, cytarabine 100 mg/m^2, gemtuzumab ozogamicin 3 mg/m^2). On day 11 after starting chemotherapy he became pyrexial (38·4°C) and was therefore commenced on broad spectrum antibiotics. A repeat chest X-ray at this time showed features of bilateral airspace opacification. Combined nose and throat swabs were negative for a respiratory virus panel by polymerase chain reaction (PCR); SARS-CoV-2 was not detected when tested retrospectively. On day 22, rigours, tachycardia and desaturation prompted transfer to ICU for high flow oxygen at a FiO_2 of 35%. On admission to ICU the serum ferritin was >100 000 μg/l, along with raised triglycerides (2·9 mmol/l), a coagulopathy (INR 1·66) and a pancytopenia. The H Score was calculated as 195 and he was started on subcutaneous anakinra 100 mg TDS, dexamethasone and IVIg. Along with a reduction in temperature, the ferritin reduced to 35 760 μg/l four days after starting anakinra and the oxygen requirements began decreasing after five days. After seven days in ICU he was discharged back to the ward, where anakinra and steroids were progressively reduced. HRCT prior to discharge showed bilateral ground glass changes with patchy distribution and small areas of peribronchial consolidation, consistent with COVID-19 (Fig 1B).

Patient three

A 36-year-old man with acute lymphoblastic leukaemia (ALL) presented with collapse and fever five days post completion of a second cycle of blinatumomab to eliminate minimal residual disease prior to allogeneic stem cell transplantation. Laboratory tests showed a lymphopenia ($0{\cdot}62 \times 10^9$/l) and a mild thrombocytopenia (121×10^9/l). Broad spectrum antibiotics were commenced. The patient desaturated two days later and combined nose and throat swabs sent for SARS-CoV-2 reverse transcription (RT)-PCR were found to be positive. A HRCT on day 11 showed widespread ground glass changes (Fig 1C). The ferritin rose to 8 961 μg/l along with a significantly rising C-reactive protein, increasing oxygen requirements and persistent pyrexia. He became progressively pancytopenic, with high triglycerides (3 mmol/l), a coagulopathy (INR 1·44) and an H Score calculated as 204. Anakinra was started at 200 mg intravenously twice a day. Initially, the ferritin continued to rise to a peak of 25 382 μg/l and the platelets continued to fall. Ten days after starting anakinra the patient defervesced and oxygen requirements were sustainably reduced. Anakinra was weaned and the clinical picture continued to improve on the ward before discharge 31 days after admission.

Discussion

We highlight that severe COVID-19 pneumonia can result in a life-threatening hyper-inflammatory syndrome in haematology patients post chemoimmunotherapy. In these patients, IL-1 blockade with anakinra was safe and resulted in clinical improvement. All three cases support the importance of screening for hyper-inflammatory states in patients with COVID-19 and acute leukaemia and support the use of immunomodulatory agents for patients with this phenotype. At this stage of the pandemic, results of large randomized trials are not available and evidence-based treatment protocols have yet to be established. Emerging evidence suggests that immunomodulatory agents such as anakinra, may improve outcomes in hyper-inflammatory COVID-19. We provide further evidence of the utility of this agent in the clinical context described and are the first to report its safe administration in patients with acute leukaemia affected by COVID-19.

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Conflicts of interest

None of the authors had relevant conflicts of interest.

James W. Day[1,2]
Thomas A. Fox[1,2]
Richard Halsey[1]
Ben Carpenter[1]
Panagiotis D. Kottaridis[1]
[1]Department of Haematology, University College London Hospitals NHS Foundation Trust and [2]UCL Institute of Immunity and Transplantation, UCL, London, UK.
E-mail: james.day@ucl.ac.uk

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Real-world assessment of the clinical impact of symptomatic infection with severe acute respiratory syndrome coronavirus (COVID-19 disease) in patients with multiple myeloma receiving systemic anti-cancer therapy

Dear Editor,

Infection with the novel coronavirus SARS-CoV-2, resulting in an acute respiratory disease (COVID-19), is the cause of the current pneumonia pandemic, with a rapid rise in cases being reported in the European Union and UK.[1,2] The UK index case was identified on January 31, 2020 and, given the rapid spread and high mortality rate of COVID-19, it is imperative to define the impact on patients with co-existing medical conditions.[3]

Multiple myeloma (MM), the second-most common haematological malignancy, is a cancer of the mature B-cell lineage, and is associated with both cellular and humoral immune dysfunction that renders patients susceptible to infections, especially of the respiratory tract.[4-7] This, coupled with a median age at presentation of 70 years in a population with frequent co-existing medical conditions, means the outcomes of MM patients infected with COVID-19 warrants particular attention. We conducted a fully-anonymised prospective clinical audit where only MM patients with documented symptomatic COVID-19, whether managed in the inpatient or outpatient setting, were reported. All patients were tested within the secondary care setting and were receiving systemic anti-cancer therapy (SACT).

At the time of analysis (May 18, 2020), 75 completed proformas from MM patients who tested swab-positive for COVID-19 had been received (Table I). The median age of COVID-19-positive MM patients was 73 years (range, 47–88), with 27·5% of patients >80 years of age. Where ethnicity details were available (n = 51), most (82%) were Caucasian, with 16% being Afro-Caribbean. 41% of patients were newly-diagnosed MM receiving frontline therapy (NDMM); 24% had relapsed from their frontline therapy and were now receiving second-line therapy (1st REL); and 35% had relapsed and/or refractory disease (RRMM). The median absolute lymphocyte count at presentation with COVID-19 symptoms was 600 cells/μl (range, 0–2500), with 90% of patients demonstrating hypo-gammaglobulinaemia affecting at least 1 sub-class (IgG> IgM>IgA). The male/female ratio was 1·5, but varied with age (<75 years ratio 2·33 vs. >75 years ratio 0·94) as a consequence of significant age difference between the groups (P = 0·049).

The median time from the UK Index case to COVID-19 symptoms was 54 days (range, 23–88). 20·5% of patients did not have a temperature on presentation but did have a cough, and 16% reported GI symptoms, with 20·5% of patients acquiring COVID-19 whilst an inpatient for other reasons. 75% had evidence of pulmonary infiltrates primarily detected by chest radiograph. All but three patients were admitted for clinical care. Systemic anticancer therapy (SACT) was stopped a median of 0·5 days (range, 5–23) after the onset of COVID-19 symptoms. Only nine of 70 patients received critical care support, with five patients requiring non-invasive ventilation, two of whom escalated to invasive ventilation and four patients going straight to invasive ventilation, with all nine patients dying. Six patients had clinical/laboratory features of cytokine release syndrome.[8,9] One patient was treated with ruxolitinib, but did not survive; one patient received tocilizimab (recovered); and four patients received supportive care only, none of whom survived. Only one patient received treatment with hydroxychloroquine.