Author contributions

DRJA was involved in the study concept and design, analysis and interpretation of data, review of the literature and prepared the first draft of the manuscript. FA and AS collected the data and reviewed the manuscript. MLinterpreted the data, reviewed the literature and revised the manuscript. MS interpreted the data and reviewed the manuscript. All authors approved the final version of the manuscript.

Conflicts of interest

The authors state that they have no conflict of interest.

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Remdesivir during induction chemotherapy for newly diagnosed paediatric acute lymphoblastic leukaemia with concomitant SARS-CoV-2 infection

The COVID-19 pandemic potentially makes treatment of acute leukaemia more difficult. Most induction chemotherapy regimens for acute leukaemia lead to extended periods of cytopenia and immunosuppression rendering patients vulnerable to opportunistic infections. As with many aspects of SARS-CoV-2, there is no universally accepted way of treating patients who present with acute leukaemia and associated infection. The limited data available so far on the outcomes of patients with cancer presenting with COVID-19 suggest they have increased risk of complications and mortality.[9] Paediatric patients exhibit milder symptoms of COVID-19 and a less severe disease course but there are little data available on paediatric haemato-oncology patients.[1,4,5,8] The optimal treatment of children with cancer and concurrent COVID-19 is unclear and requires case by case discussion with individualised management plans. Several different antiviral and immunomodulatory therapies have been trialled in patients presenting with COVID-19. Remdesivir (GILEAD, Foster City, CA, USA) has shown *in vitro* activity against SARS-CoV-2, the virus that causes COVID-19. The data available on use suggest clinical benefit, with recent guidelines recommending consideration of its use in severe infections.[2,7,11] There is limited evidence on safety in paediatric use of remdesivir. However, adult data are reassuring from a safety perspective, with major adverse events described being transaminitis and nausea.[2,6,10]

We report the use of remdesivir in a previously well five-year-old child diagnosed with precursor B-cell acute lymphoblastic leukaemia and concomitant SARS-CoV-2 infection. He was hospitalised with a short history of fever,

petechiae and neck swelling. On initial assessment he was found to have large bilateral neck swelling with associated swollen lip and tongue. He had inspiratory stridor, and oxygen saturations were normal. He was initially treated with nebulised adrenaline and a single dose of oral dexamethasone. A chest X-ray performed showed perihilar bronchial thickening with no other changes. Initial blood results showed anaemia with a haemoglobin level of 57 g/l, a platelet count of 55×10^9/l and a total white cell count of $6{\cdot}76 \times 10^9$/l. Circulating blasts were present on the peripheral blood film and flow cytometry on peripheral blood confirmed precursor B-cell acute lymphoid leukaemia (ALL), NCI standard risk. He was transferred to the paediatric intensive care unit (PICU) due to concerns about need for airway support. Nasopharyngeal aspirate on admission to PICU was positive on SARS-CoV-2 RNA polymerase chain reaction (PCR) performed on the QIAstat respiratory SARS-CoV-2 panel (QIAGEN, Hilden, Germany), an assay with a 2-h turnaround in our in-house laboratory. Further history from the parents revealed they themselves had symptoms consistent with COVID-19 (high fevers, cough and anosmia) three weeks previously. Multidisciplinary team discussion between infectious diseases, haematology, pharmacy and PICU teams and an infectious diseases team from an external centre led to the decision to treat him with remdesivir for fivedays. Our trust had also set up a system in collaboration with the bioethics committee for expedited consideration and approval of unlicensed drugs in the context of the pandemic. The decision to treat was made because the patient was thought to be in the early stages of infection with SARS-CoV-2 and his need for urgent chemotherapy would lead to significant immunosuppression, due to high-dose prolonged dexamethasone. There are no described significant predicted drug interactions between remdesivir and ALL induction chemotherapy (dexamethasone, vincristine and pegylated asparaginase) as per https://www.covid19-druginteractions.org. His stridor settled without further intervention and he had a general anaesthetic for insertion of a Portacath, bone marrow aspirate, diagnostic lumbar puncture and intrathecal methotrexate. Cytogenetics confirmed *ETV6-RUNX1* rearrangement and cerebrospinal fluid was negative for leukaemic cells. Remdesivir was obtained on the compassionate access programme from Gilead and started on day two of admission. Paediatric dosing for remdesivir is not yet established and current treatment protocols are based on dosing for ebola. Our patient was treated initially with a loading dose of remdesivir at 5 mg/kg intravenously, followed by 2.5 mg/kg daily.[3] Chemotherapy as per UKALL 2019 interim guidelines three-drug induction (regimen A therapy consisting of pegylated asparaginase, intrathecal methotrexate, vincristine and dexamethasone) was started the same day as remdesivir initiation.

He was monitored with daily blood tests including liver function testing during treatment. On day 3 his alanine amino-transferase (ALT) began to increase from a normal level at diagnosis, reaching a peak of 408 U/l (upper limit of normal 25 U/l) on day 5. His alkaline phosphatase, albumin and bilirubin remained within normal limits. Although raised ALT is an expected finding during induction chemotherapy, remdesivir was discontinued as stipulated by the compassionate use guidelines; the patient had at this point completed four out of the planned five days of treatment. Repeat SARS-CoV-2 testing by PCR on naso–pharyngeal aspirate (NPA) at this point was negative, and he was found to have SARS-CoV-2-specific IgG antibodies in serum as tested by ELISA (Epitotpe Diagnostics Inc, San Diego, CA, USA). Stool was test weekly in the first month and remained negative by PCR for SARS-CoV-2. Following cessation of remdesivir, ALT returned to normal limits within 10 days. During his admission, he maintained normal saturations without requiring supplemental oxygen therapy. He had no further temperatures after starting remdesivir. He was discharged home on day 8 of induction and had no further unplanned admissions during induction. End of induction assessment showed his bone marrow in morphological remission with undetectable minimal residual disease. SARS-CoV-19 testing by PCR remains negative.

This is the first case described in the United Kingdom of treatment of a child with a new presentation of acute leukaemia and SARS-CoV-2 infection treated with antiviral therapy. He remained asymptomatic from SARS-CoV-2 and did not deteriorate with immunosuppressive chemotherapy. His initial low viral load, coupled with the timing of his parents' symptoms of COVID-19 suggests that he had SARS-CoV-2 infection for some time prior to presentation with ALL. However, his risk of progression to severe infection was significant due to initiation of chemotherapy and high-dose steroids. Remdesivir therapy could be useful in similar high-risk periods or pre-emptively following exposure to SARS-CoV-2. In this case, remdesivir was well tolerated with no side effects except anticipated elevation in ALT which was more likely secondary to induction chemotherapy. It demonstrates the need for regular monitoring of liver function tests during therapy, as well as the difficulty of assessing safety profiles of medications when started in the acute phase of an illness when chemotherapy agents are started concurrently. On balance in this case remdesivir was discontinued as the child had clinically improved and SAR-CoV-2 PCR was negative. Further studies are needed to assess the safety and efficacy of SARS-CoV-2 therapies in paediatric haematology patients with both symptomatic and asymptomatic infection.

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Author contributions

All the authors provided clinical care for the patient and were involved in critically revising the manuscript. All the authors have approved the final manuscript.

Conflicts of interests

AB has completed paid consultancy work for Gilead relating to the management of COVID-19 in children.

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Thrombocytopenia is independently associated with poor outcome in patients hospitalized for COVID-19

Thrombocytopenia (defined by platelet count $<150 \times 10^9$/l) has been observed in up to 36% of patients with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19).[1] In this setting, thrombocytopenia is usually mild, caused by platelet activation and consumption.[2,3] In a recent paper published in the British Journal of Haematology, Jiang *et al*[4] conducted a meta-analysis of 31 studies involving 7613 participants and found a significant association between thrombocytopenia and patients hospitalized