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RAPID COMMUNICATION

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ChAdOx1 SARS-CoV-2 vaccination: A putative precipitant of adrenal crises

Deirdre Maguire[1] | David S. McLaren[2] | Irum Rasool[1] | Preet M. Shah[1] | Julie Lynch[2] | Robert D. Murray[2,3]

[1]Department of Diabetes and Endocrinology, Harrogate Hospital NHS Foundation Trust, Harrogate, UK

[2]Department of Endocrinology, Leeds Centre for Diabetes and Endocrinology, St James's University Hospital, Leeds, UK

[3]Leeds Institute for Cardiovascular and Metabolic Medicine (LICAMM), Faculty of Medicine and Health, School of Medicine, University of Leeds, Leeds, UK

Correspondence
Robert D. Murray, Leeds Centre for Diabetes and Endocrinology, Leeds Teaching Hospitals NHS Trust, St James's University Hospital, Beckett St, Leeds LS9 7TF, UK.
Email: robertmurray@nhs.net

Abstract

Background: Patients with adrenal insufficiency (AI) have excess mortality, in part due to the occurrence of life-threatening adrenal crises. Infective processes, including that of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), are recognised as the major precipitant of adrenal crises. Adverse reactions to the ChAdOx1 SARS-CoV-2 vaccine occur in a significant proportion of individuals, however, are mild-moderate in the majority of cases.

Design: Case series.

Patients & Results: We describe five cases where more severe adverse reactions to the ChAdOx1 SARS-CoV-2 vaccine led to actual or incipient adrenal crises requiring parenteral hydrocortisone within 24 h of receiving the first ChAdOx1 SARS-CoV-2 vaccination.

Conclusion: In individuals with adrenal insufficiency, adverse reactions to the initial dose of the ChAdOx1 SARS-CoV-2 vaccination can precipitate adrenal crises. We recommend that patients with AI should immediately increase their maintenance glucocorticoid dosage 2–3 fold on experiencing any symptoms in the initial 24 h following vaccination.

KEYWORDS
adrenal crisis, adrenal insufficiency, COVID-19, SARS-CoV-2, vaccination

1 | BACKGROUND

The hallmark of coronavirus (coronavirus disease 2019 [COVID-19]) infection leading to clinical deterioration has been the associated severe cytokine storm. Improvement in numbers of cases, hospital admissions and deaths have been cognisant on periods of 'lockdown' and the role out of various highly efficacious coronavirus vaccines at a population level. Vaccines in usage have utilised different methodologies including messenger RNA vaccines (Pfizer, Moderna) and adenovirus vectors (AstraZeneca [AZ]).[1–3] Immediate and early adverse reactions to the vaccines that have been reported are generally mild to moderate.[1–4] Cases of more serious complications including the well-publicised thromboembolic complications associated with the AZ vaccine and anaphylaxis with the Pfizer vaccine have fortunately been rare.

Patients with adrenal insufficiency (AI) are considered at increased risk of infections and have a longer duration of recovery.[5] Infections are also the most frequent precipitant of life-threatening adrenal crises (ACs).[6,7] In the United Kingdom, therefore, AI has therefore been considered as an indication for early vaccination. At the onset of significant infections patients with AI are taught to increase their maintenance steroid dosage, generally 2–3 fold. This advice is not usually suggested for patients with AI when undergoing vaccinations. We describe five cases of adrenal crises (requiring parenteral glucocorticoids and

intravenous fluids)[8] or incipient crises (requiring parenteral glucocorticoids) resulting from the first dose of the ChAdOx1 SARS-CoV-2 vaccination. All patients provided consent for the publication of the data.

1.1 | Case series

Case 1: 66-year-old female with Addison's disease (AD) and primary hypothyroidism on maintenance hydrocortisone (HC) 20 mg/day in divided doses, fludrocortisone (FC) 100 mcg od and levothyroxine 87.5 mcg od. She underwent vaccination at 11 AM, remaining well through the afternoon and evening. She woke at midnight generally unwell, unsteady on her feet and suffered vivid dreams overnight. On waking the following morning she remained unwell with headache, severe fatigue and felt she was going to have a 'crisis'. She took HC 20 mg, however, appeared so unwell her daughter called an ambulance who on arrival administered HC 100 mg IM and she was taken to the local hospital emergency department. Her observations at 9 AM showed a temperature of 39.7°C, blood pressure (BP) 133/66 mmHg, glucose 3.6 mmol/L, and O_2 saturations 92%. A chest X-ray was clear, urea and electrolytes and inflammatory markers were normal. The oxygen therapy was weaned over around 5 h and she was discharged on a double dose of HC for 2 days.

Case 2: Gentleman with known AD and short bowel syndrome secondary to mesenteric panniculitis on maintenance HC 30 mg/day in divided doses and FC 100 mcg od. He received the AZ vaccine in the evening and was well until waking at 3 AM with generalised abdominal cramps, watery diarrhoea, nausea and anorexia, to the extent he could not take his morning HC. He, therefore, presented himself to the local hospital. At assessment he was visibly unwell, BP 91/52 mmHg, temperature 38.3°C, with dry mucous membranes. He was commenced on HC 50 mg bd and IV fluids. His HC was weaned over the next few days as his abdominal symptoms settled. Once eating he was commenced back on his normal maintenance HC and FC.

Case 3: A 69 years female with autoimmune polyglandular syndrome type 2 (AD, type 1 diabetes mellitus, premature ovarian insufficiency, vitiligo, thyroidectomy) receiving HC 20 mg/day, FC 100 mcg od, levothyroxine 100 mcg od, dehydroepiandrosterone 25 mg od, and insulin. She received her vaccination mid-morning and remained well until 6 AM the following morning. At that time she experienced general malaise, lethargy and diarrhoea. She was unsteady on her feet and collapsed. She took a further 10 mg HC without perceived benefit and therefore went on to take her HC 100 mg intramuscularly at 8.40 AM, followed by a twofold increase in her normal daily HC dosage for 2 days. Following improvement with intramuscular HC she decided not to attend medical services.

Case 4: A 41-year-old woman who underwent transsphenoidal surgery (TSS) in 2012 for Cushing's disease and who had been rendered panhypopituitary. She currently takes dual-release HC 15 mg od, growth hormone 0.3 mg nocte, levothyroxine 100 mcg od, liothyronine 20 mcg od, desmopressin nasal spray 10 mcg nocte and hormone replacement therapy. During intercurrent illness she has been instructed to take immediate release HC 10 mg tds. She received her vaccination around midday and remained well through the afternoon. At 9 PM she came over very lethargic with abdominal and back discomfort. At 11 PM she woke with general malaise, a high temperature, sweats, headache and vomiting. Additional HC was vomited back, she started feeling 'delirious' and therefore called the emergency services. She received HC 100 mg IM by the paramedics and again on arrival in hospital with additional IV fluids. She remained an in-patient overnight and was discharged the following day.

Case 5: A 74-year-old man who underwent TSS for a non-functioning pituitary adenoma with resultant anterior hypopituitarism. Daily replacement therapy included HC 15 mg, levothyroxine 137.5 mcg, and testosterone gel 40 mg. Vaccination was performed at 10 AM with the onset of general malaise and feeling cold around 5 h later. By the late evening, there had been the onset of increasing malaise, nausea, vomiting, a high temperature and confusion. Further oral HC was vomited back and his wife, therefore, administered HC 100 mg IM. They decided to observe to see if he showed any improvement from this before attending the local hospital. By the next morning he had improved considerably, was able to take his oral HC and increased his dosage twofold for 3 days.

2 | DISCUSSION

We describe five cases of adrenal crisis/incipient crisis within the first 24 h after administration of the first dose of the AstraZeneca ChAdOx1 SARS-CoV-2 vaccine. The temporal association between the ChAdOx1 SARS-CoV-2 vaccination and actual or incipient adrenal crises in this small series is highly suggestive that the COVID-19 vaccine is a plausible precipitant of adrenal crises.

The ChAdOx1 SARS-CoV-2 vaccine utilises a recombinant, replication-deficient chimpanzee adenovirus vector to facilitate delivery of the genetic code of the SARS-CoV-2 spike glycoprotein into the host cells. The spike protein is produced within the cells initiating specific induction and activation of the immune system. This vaccine technology has been previously used in the construction of vaccines for influenza and Middle East respiratory syndrome. In clinical studies of the ChAdOx1 SARS-CoV-2 vaccine adverse reactions were injection site tenderness (63.7%) and pain (54.2%), headache (52.6%), fatigue (53.1%); myalgia (44.0%), malaise (44.2%); pyrexia (feverishness [33.6%] and fever ≥38°C [7.9%]), chills (31.9%), arthralgia (26.4%) and nausea (21.9%).[1,4] Adverse reactions tended to be mild to moderate in severity, resolved within a few days of vaccination, and are less frequent and severe with the second dose.[1,4]

Patients with both primary and secondary AI have been shown to have increased mortality and morbidity[9,10] contributed to, in part, by the occurrence of adrenal crises. The incidence of ACs has been reported to be 5.2–17 per 100 patient-years in PAI and 3.6–5.8 per 100 patient-years in SAI.[6,7,11,12] Adrenal crises have been estimated to be fatal in around 6% of cases.[7] Infectious diseases, particularly gastroenteritis, are reported to be the most common precipitating factors for ACs.[6,7,11] Individuals with AI have higher rates of infections leading to more frequent hospital admissions.[5] Emotional stress, missed glucocorticoid doses or inadequate glucocorticoid dose escalation for intercurrent illness may also be factors facilitating ACs.[7,13]

Similar to other infective processes, our case series suggests the acute onset of often quite marked adverse reactions following the ChAdOx1 SARS-CoV-2 vaccine, including high fever and associated stresses are able to precipitate adrenal crises. In fact, the symptoms described by our cohort mirror those experienced by subjects in the initial efficacy studies of the ChAdOx1 SARS-CoV-2 vaccine. None of our patients pre-empted the possibility that the vaccination could lead to a potential adrenal crisis, and therefore did not increase their maintenance HC dosage beforehand. The management of AI in the patients in this series were reflective of UK practice.[14,15] All the individuals were on appropriate HC replacement regimens, had undergone regular education as to 'sick day' rules for managing their HC during intercurrent illness and stresses, had IM HC for emergency usage, and had been taught how to administer this.

The patients in this series came to attention over a period of four months; two during presentation at the emergency department, whereas the additional three patients contacted the endocrine specialist nurse following the event. Unfortunately, this series does not allow us to determine the incidence of occurrence of actual or incipient adrenal crises following ChAdOx1 SARS-CoV-2 vaccination within our cohort of patients with AI (n = ~500) as the number vaccinated, vaccine type utilised, and whether further cases have occurred but presented to local hospitals is not currently known. Furthermore, although all subjects had received the ChAdOx1 SARS-CoV-2 vaccine in this series, this likely reflects the distribution of the vaccine and its usage within the United Kingdom. We are therefore unable to determine if alternate vaccines might similarly result in adrenal crises. In line with recommendations from the Addison's Disease Self Help Group (ADSHG), we strongly recommend that individuals with known AI immediately increase their maintenance glucocorticoid dosage 2–3 fold for 24 h should they experience any symptoms after receiving their COVID-19 vaccination.[16] It is also imperative that patients check they have HC for injection, that this is in date and are they or a close relative are confident in its usage before undergoing vaccination.

AUTHOR CONTRIBUTIONS

The cases series was proposed by DM and RDM which was then discussed between all authors. DSM, IR, PMS and JL brought together the clinical summaries and consented the patients. The initial manuscript was written by RDM. All authors reviewed and contributed to finalising the manuscript.

CONFLICT OF INTERESTS

Deirdre Maguire, David S. McLaren, Irum Rasool, Preet M. Shah have no conflict of interests. Robert D. Murray has received honoraria for consultancy from Shire/Takeda and is on the steering committee of the European Union Adrenal Insufficiency Registry.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Robert D. Murray http://orcid.org/0000-0001-6730-6109

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