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Systemic listeriosis following vaccination with the attenuated *Listeria monocytogenes* therapeutic vaccine, ADXS11-001

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Dear Editor

We describe a case of systemic listeriosis during a phase I trial of ADXS11-001 (axalimogene filolisbac) in Human papillomavirus (HPV)-positive oropharyngeal cancer (OPC).

ADXS11-011 is a novel therapeutic vaccine under investigation in HPV-associated malignancies[1]. ADXS11-001 is a live, bioengineered *Listeria monocytogenes* (Lm) vector containing a plasmid insert (pGG55) which, *inter alia,* facilitates secretion of HPV genotype-16 (HPV-16) E7 oncoprotein fused to an attenuated Lm virulence factor, Listeriolysin O. ADXS11-001 induces immune responses in HPV-related cancers through multiple mechanisms of action [1, 2].

Clinical testing of ADXS11-001 is most advanced in cervical cancer[1], in which HPV-16 has a causal role[3]. HPV-16 is associated with other malignancies, including OPC, in which there has recently been a rapid rise in incidence. Although HPV-related OPC is usually cured following multi-modality treatment, a not insignificant number of patients develop recurrent/metastatic disease. In addition, current standard-of-care treatments have long-term functional consequences with negative impact on quality-of-life. Therefore, novel therapeutic agents that will improve survival and/or reduce the incidence of adverse events are urgently needed. Following encouraging data from trials in cervical cancer, we initiated a dose-escalation phase I trial of ADXS11-001 in patients treated with curative intent for locally-advanced HPV-16-positive OPC (REALISTIC - NCT01598792), the primary endpoint of which was to establish the

safety and toxicity profile of the vaccine in this clinical setting. (https://clinicaltrials.gov).

Patient 1 was enrolled in October 2013, and received two vaccinations at dose-level 1 ($3.3x10^8$ colony-forming units (CFU)) without unexpected adverse effects. Patient 2 was a 61 year old man with a past history of treated hypertension and hypercholesterolemia. He had undergone transoral laser surgery, followed by post-operative radiotherapy, for T2N2aM0 OPC 16.5 months previously. His ECOG performance status was 0 on trial entry.

Approximately 3.5 hours after intravenous (iv) administration of $3.3x10^8$ CFU ADXS11-001, he developed headache and generalised flu-like symptoms, although all observations were normal. Acetaminophen (1g) was given iv with clinical benefit. Similar symptoms, with normal observations, recurred at 6.5 hours post-infusion and resolved with 1g iv acetaminophen. At 8.5 hours post-infusion, the patient became unwell and pyrexial (38.1°C) with a tachycardia (93 bpm). Symptoms failed to settle with further acetaminophen and he became nauseated and vomited. Over the next 6 hours, symptoms and vital signs, whilst fluctuating, were within the range expected from previous safety data and were controlled by conservative measures (acetaminophen, ondansetron).

At 14.5 hours post-vaccination his clinical condition deteriorated significantly, with pyrexia (39.1°C), tachycardia (106 bpm) and profound nausea/vomiting. At this point, per protocol, 2g iv ampicillin QDS and iv fluids were initiated and he was transferred to the Infectious Disease Unit (IDU). Clinical examination and investigations revealed

left basal pneumonia. Sequential blood tests confirmed elevated alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (γGT), peaking at 131 U/L (NR: 7-55U/L) and 256 U/L (NR: 0-45 U/L), respectively, on day 7 post-vaccination. The patient's condition improved and he was fit for discharge 7 days after admission to the IDU. Liver enzymes returned to normal over several weeks.

Per protocol, blood was taken for culture 5 hours post-vaccination and was negative for bacterial growth after 72 hours. However, repeat blood culture, immediately before institution of antibiotics, grew *Listeria monocytogenes* with identical antibiotic resistance to ADXS11-001 (chloramphenicol resistance conferred by pGG55 plasmid insert). Four subsequent blood cultures and a stool test were negative for *Listeria monocytogenes*. Chest radiograph after discharge was clear. cANCA/pANCA were negative, Ig profile was normal and there was no paraprotein on electrophoresis. Importantly, the patient has had no recurrence of symptoms since discharge and remains well 20 months post-vaccination with ADXS11-001.

Following this serious adverse event, the trial was immediately put on hold. Following consultation with the vaccine manufacturer (Advaxis), the trial was terminated early. To our knowledge, no other cases of listeriosis have been reported following ADXS11-001.

Although we did not confirm sequence identity between the pathogen grown at blood culture and ADXS11-001, the chronology of events and pattern of antibiotic resistance point to the fact that systemic listeriosis was caused by the study drug. Internal review of the temperature log of the freezer where vaccine was stored

confirmed several minor temperature excursions (highest temperature -52°C for 20 minutes) in the period before vaccination. An internal enquiry undertaken by the sponsors and accepted by the UK Medicines and Healthcare Regulatory Agency, found no relationship between the temperature deviations and the occurrence of systemic listeriosis.

In conclusion, we highlight a potential adverse event of attenuated Lm vectors and urge caution on the part of investigators working with such agents.

References

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