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CASE REPORT

Transplantation of solid organs procured from influenza A H1N1 infected donors

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Summary

Following the influenza A H1N1 (swine flu) pandemic, there remains little evidence informing the safety of transplanting organs from donors suspected or diagnosed with H1N1. Limited guidelines from the major transplant societies leave the use of such organs at the discretion of individual transplant centres, and practice varies considerably both nationally and internationally. We present the largest published series of outcome following transplantation of organs from H1N1 positive donors and demonstrate that these organs can be transplanted safely and with good short-term outcome. We discuss our local policy for treatment of recipients with Oseltamivir.

Introduction

The influenza A H1N1 (herein 'H1N1') pandemic posed unique dilemmas for transplant programmes, with concern for diagnosis and treatment of H1N1 in transplant recipients, who were presumed to be at increased risk of severe infection compared with immunocompetent individuals. There was also concern over potential H1N1 transmission when transplanting organs from infected donors.

The risk of transmission of H1N1 from donor to recipient remains to be established. We identified only one case report of two transplant recipients receiving a kidney from the same H1N1 positive donor. The recipients underwent transplantation at different transplant centres, were managed differently in their postoperative course, and both had uneventful recoveries [1]. Herein, we present four patients who received organs (three kidney, one liver) from H1N1 positive donors. To the best of our knowledge, this is the largest published series of outcome following solid organ transplantation from H1N1 positive donors, and the only published case of outcome following liver transplantation from an H1N1 positive donor.

Case reports

Case 1

A 24-year-old man with end-stage renal disease secondary to pyelonephritis received a renal transplant from a 40-year-old brainstem death (DBD) donor. The donor had died of hypoxic brain injury secondary to H1N1-induced respiratory failure and had received 4 days of Oseltamivir 150 mg twice daily prior to organ procurement. Compatibility was 0 HLA mismatch and cold ischaemic time (CIT) was 16 h 34 min. Immunosuppression was initiated with methylprednisolone and alemtuzumab on induction, and maintained on tacrolimus monotherapy. Oseltamivir treatment was not instituted postoperatively because

donor treatment was judged by the implanting team to be adequate such that the risk of disease transmission was very low. He had not previously received swine flu vaccination. He made a good postoperative recovery, with no clinical signs or symptoms of viral illness or upper respiratory tract infection. There was primary graft function and he was discharged on postoperative day 7. Graft function remains good 20 months post-transplant.

Case 2

A 48-year-old man with autosomal dominant polycystic kidney disease received a renal transplant from a 51-year-old cardiac death (DCD) donor. The donor, who had a history of myotonic dystrophy, died from H1N1 pneumonia. She had received 3 days of Oseltamivir 75 mg twice daily prior to organ procurement. Compatibility was 4 HLA mismatch (2 A; 1 B; 1 DR) and CIT was 14 h 26 min. Immunosupression was initiated with methylprednisolone and basiliximab on induction, and maintained on tacrolimus and mycophenolate dual therapy. There was delayed graft function requiring two episodes of haemodialysis postoperatively. He received a single dose of Oseltamivir 30 mg orally immediately postoperatively, and continued a 5-day course of treatment dose Oseltamivir adjusted according to renal replacement therapy (Table 1). He had previously received swine flu vaccination 1 year prior to transplantation. Postoperative recovery was good with no clinical signs or symptoms of viral illness or upper respiratory tract infection. He was discharged on day 12. Graft function remains good 8 months post-transplant.

Case 3

A 59-year-old man with end-stage renal disease secondary to autosomal-dominant polycystic kidney disease received the paired kidney from the DCD donor in Case 2. Compatibility was 3 HLA mismatch (1 A; 1 B; 1 DR) and CIT was 20 h. Immunosupression was initiated with methylprednisolone and basiliximab at induction, and continued with tacrolimus and mycophenolate dual therapy. There was delayed graft function requiring two sessions of peritoneal dialysis. He received a single dose of Oseltamivir 30 mg orally immediately postoperatively, and continued a 5-day course of treatment dose Oseltamivir adjusted according to renal replacement therapy (Table 1). He had previously received swine flu vaccine 1 year prior to transplantation. There were no clinical signs or symptoms of viral illness or upper respiratory tract infection, and he was discharged on postoperative day 11. Graft function remains good 8 months post-transplant.

Case 4

A 63-year-old man with nonalcoholic steatohepatitis cirrhosis, MELD 15, received a liver transplant from a 50-year-old DCD donor, who had died of hypoxic brain injury following hanging. CIT was 7 h. There was primary nonfunction of the graft and the patient remained ventilated and on haemofiltration whilst re-listed for a super-urgent transplant. The following day, he received a re-graft from a 21-year-old DBD donor, who had died of presumed bacterial meningitis on the basis of clinical presentation and high white cell count in cerebrospinal fluid on lumbar puncture. The donor had received one dose of Oseltamivir on admission as empirical treatment for possible H1N1, together with Ceftriaxone for presumed meningitis. CIT of the re-graft was 5 h. The donor was confirmed as H1N1 positive after implantation of the liver in the recipient. Immunosuppression was initiated with basiliximab, and maintained with tacrolimus, mycophenolate and prednisolone triple therapy. The patient

Table 1. Guidelines followed in Leeds Teaching Hospitals NHS Trust for the dosing of Oseltamivir (Tamiflu®) in patients with renal failure and following transplant. We advocate full treatment dose for recipients of organs from H1N1 positive donors. Prophylactic dosing for patients with renal failure is included for comparison.

	Treatment (5 days)	Prophylaxis (10 days)
Haemodialysis (Hiflux/HDF using Rexceed dialyser)	Initial 75 mg dose then 75 mg after each dialysis session	Initial 75 mg dose then 75 mg after each dialysis session
Peritoneal dialysis	A single 30 mg dose given ideally after an exchange	A single 30 mg dose given ideally after an exchange and repeated after 7 days
Continuous renal replacement therapy	75 mg daily or 30 mg twice daily	75 mg on alternate days or 30 mg daily
CrCl >30 ml/min	75 mg twice daily	75 mg once daily
CrCl 10–30 ml/min	75 mg daily or 30 mg twice daily	75 mg on alternate days or 30 mg daily
CrCl <10 ml/min not on dialysis	Single 30 mg dose	Single 30 mg dose
Haemodialysis (using APS dialyser)	Initial 30 mg dose then 30 mg after each dialysis session	Initial 30 mg dose then 30 mg after each dialysis session

remained on the Intensive Care Unit for 7 days, requiring 4 days of haemofiltration. Graft function remained good. He had received seasonal flu vaccine, including swine flu vaccine 3 weeks prior to transplantation, and received a 5-day course of treatment dose Oseltamivir adjusted according to renal replacement therapy post-transplantation (Table 1). He became pyrexial on postoperative day 9, and was treated for hospital-acquired pneumonia based on clinical and radiological findings. Throat swabs were negative for viral pathogens, including H1N1 by the polymerase chain reaction method. Thereafter, postoperative recovery was good and he was discharged on day 25. Graft function remains good 6 months post-transplant.

Discussion

Influenza A H1N1 was first identified in Mexico in April 2009. By July 2009, the World Health Organisation had declared a pandemic, the first in over 40 years. Although an end to the H1N1 pandemic was declared in August 2010, the 2009 H1N1 virus will probably persist for many years, similar to seasonal influenza viruses. This novel influenza strain raised particular concern in comparison with other seasonal influenza variants because of the atypical pattern of illness and death. There was a high level of illness in the summer months. Pregnant women and those with underlying chronic lung disease were particularly affected, with many requiring intensive care support. There was also an unusually high number of deaths in young, otherwise healthy, individuals.

The impact of H1N1 infection in transplant donors and recipients remains unknown. Transplant recipients are more susceptible to severe infection from influenza, with complications, including viral pneumonia, bacterial co-infection and the risk of acute graft rejection during weaning of immunosuppression [2]. Since the 2009 H1N1 pandemic, a number of case series and multicentre studies have reported the outcome of H1N1 infection in transplant patients [3–5]. The largest, a multicentre cohort study of 237 transplant patients admitted with H1N1 in 26 centres demonstrated a 16% incidence of admission to ICU and 4% mortality. Initiation of antiviral treatment within 48 h of symptom onset significantly reduced ICU admission and mortality [3]. Similar findings were observed in case series, which also reported 14–20% incidences of graft dysfunction [4,5]. One case report describes two liver transplant patients who developed acute cellular rejection following H1N1 infection [6].

In 2009, a guidance document was published on influenza H1N1 in solid organ transplantation and endorsed by major transplant societies [7]. The authors outline recommendations for the prevention, diagnosis and treatment of H1N1 in previous transplant recipients, and recommend that all solid organ transplant candidates and recipients receive the annual seasonal influenza vaccination and at least one H1N1 vaccination. However, there is limited guidance on the use of organs from H1N1 infected donors, as the risk of transmission of H1N1 to the recipient from solid organ transplantation remains unknown. *In vivo* studies have demonstrated high viral loads in lung and bowel tissue from animals inoculated nasally with H1N1 [8,9] and it is recommended not to transplant lung or small bowel from potential donors diagnosed with influenza within the preceding 2 weeks, even if they have completed a course of antiviral treatment. There are no data on the duration of donor therapy required before transplanting other solid organs, and centres are therefore advised to consider organs from H1N1 donors on a case-by-case basis. Where organs from H1N1 donors are transplanted, a 5 to 10-day course of treatment dose antiviral therapy is recommended if the donor did not complete treatment [7]. In the United Kingdom, similar guidelines were produced by the Department of Health Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) [10].

We have adopted a policy in our centre of accepting organs from H1N1 positive donors. Where donor treatment for suspected or confirmed H1N1 has been incomplete, our recipients receive full treatment dose Oseltamivir for 5 days with dose and frequency of administration titrated based on creatine clearance, or method of renal replacement therapy. In our limited experience of three kidneys and one liver transplanted from H1N1 positive donors, good short-term outcomes can be achieved. Graft function was good in all four patients, with only short periods of DGF in the two recipients of DCD kidneys. There was no clinical indication for biopsying any of the grafts and all patients were maintained on full dose immunosuppression throughout their postoperative course. Two of the four recipients had received H1N1 vaccination 1 year prior to transplantation. The third received the vaccine only 3 weeks prior to transplantation, but this is still probably long enough to have raised an immune response. Vaccination in these three patients may have conferred some protection against transmission of donor H1N1 and may have contributed to good graft outcome, although it is not possible to evaluate this further based on this case series alone. We continue to advocate seasonal influenza and at least one H1N1 vaccination for all transplant candidates and recipients.

In conclusion, based on the limited available evidence, good short-term outcomes can be achieved with select organs procured from H1N1 infected donors. Centres should not necessarily decline grafts on the ground of H1N1 positivity in donors alone. We recommend that

recipients of organs from H1N1 positive donors should receive treatment dose Oseltamivir for 5 days following transplant, unless the donor has already received a full course of treatment, in which case, no further prophylaxis or treatment in the recipient is necessary.

Authorship

LH and NA: designed the study. CE and AJC: collected the data. AJC and MJ: wrote the manuscript. All authors read and approved the final manuscript prior to submission.

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