for susceptible organisms may not be achieved consistently in patients without severe meningeal inflammation, even when high daily doses of up to 4 g are used. Therefore, some authors advocate intrathecal administration of vancomycin, although a comprehensive evaluation of the benefits has yet to be made and the associated risks, such as ototoxicity, remain unclear.2 Treatment of ampicillin-resistant enterococcal infections is further complicated by the fact that the activity of vancomycin is bacteriostatic. The CSF may not be sterilized unless bactericidal activity is established by the addition of gentamicin.3 These factors, and the desire to avoid further surgery to establish intrathecal access, made linezolid an attractive treatment option for our patient.

Linezolid is the first licensed member of the oxazolidinone class of antibiotics with activity against almost all Gram-positive pathogens. Excellent tissue penetration and 100% oral bioavailability are notable properties of linezolid and it is approved in Europe and the USA for the treatment of nosocomial pneumonia, skin and soft tissue infections and, in the USA, vancomycin-resistant E. faecium and methicillin-resistant Staphylococcus aureus (MRSA) infections.3 Linezolid has also been shown to have good penetration into the CNS.4 A 2007 review of the evidence regarding the use of linezolid for the treatment of patients with CNS infections identified 42 relevant cases. In the 39 patients in whom the responsible pathogen was isolated, those predominantly responsible for the CNS infections were: penicillin-non-susceptible Streptococcus pneumoniae (7; 17.9%), vancomycin-resistant enterococci (6; 15.4%), Nocardia spp. (5; 12.8%), methicillin-resistant Staphylococcus epidermidis (4; 10.3%) and MRSA (3; 7.7%). Of the 42 patients treated with linezolid, 38 were either cured or showed clinical improvement.3 Case reports of other authors have found that enterococci disappeared from the CSF after as little as 2 days of iv linezolid treatment.6

This case shows that linezolid may not reliably treat post-neurosurgical intracranial infections caused by enterococci even in the absence of prosthetic material.

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References


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A paediatric case of acute liver failure associated with efavirenz-based highly active antiretroviral therapy and effective use of raltegravir in combination antiretroviral treatment after liver transplantation

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Sir,
The role of antiretrovirals is often implied in liver toxicity, but they rarely cause acute liver failure (ALF). Nucleoside reverse transcriptase inhibitors (NRTIs) are associated with mitochondrial toxicity, which can lead to lactic acidosis with ALF. Protease inhibitors (PIs) and non-NRTIs (NNRTIs) can cause liver toxicity, especially in patients co-infected with viral hepatitis. Nevirapine is the NNRTI most commonly associated with ALF.1 There is only one reported case of ALF associated with efavirenz-based antiretroviral therapy (ART).2 In patients with HIV who develop liver failure and require liver transplantation, the choice of ART after liver transplantation is limited because of interactions between ART and immunosuppressants and adverse effects on renal and liver functions.

We report for the first time a paediatric HIV case requiring liver transplantation for ALF 13 weeks after starting efavirenz-based ART and being treated with raltegravir post-transplantation. Consent for publication of this case was given by the parents of the child.

The patient was born in the UK by normal delivery and was breast-fed. Antenatal screening for HIV infection was declined. HIV infection was diagnosed at 8 months of age when he presented with generalized lymphadenopathy, massive abdominal
distention with hepatosplenomegaly, oral thrush and weight loss. A liver biopsy showed fatty liver. Baseline CD4 count was 1239 cells/mm³ (38%) and viral load (VL) was 150 000 copies/mL. He was started on zidovudine, didanosine, nelfinavir and co-trimoxazole prophylaxis, on which he remained well with undetectable VL and CD4 count of 1507 cells/mm³ (40%).

At 9 years of age, he started a structured treatment interruption, but 10 months later, he developed recurrent pharyngitis and generalized lymphadenopathy; his CD4 count fell to 446 cells/mm³ (14%) and VL increased to 20 600 copies/mL. He was restarted on ART with Kivexa (lamivudine + abacavir) and efavirenz but developed a rash shortly afterwards, thought to be due to abacavir, and treatment was stopped. After the rash settled, lamivudine and efavirenz were restarted, and zidovudine was substituted for abacavir. Subsequently, human leucocyte antigen (HLA) typing showed that he was HLA B5701-negative. His CD4 count recovered in 8 weeks to 1121 cells/mm³ (31%) and VL became undetectable. Liver function tests (LFTs) 2 weeks after restarting ART were normal.

Thirteen weeks after restarting ART, he developed jaundice, preceded by vomiting and fever, and hepatomegaly. His LFTs and clotting were severely deranged: aspartate aminotransferase (AST), 2753 IU/L [normal value (nv) < 50]; alkaline phosphatase (ALP), 793 IU/L [nv < 455]; bilirubin, 138 µmol/L [nv < 20] (conjugated bilirubin, 108 µmol/L); and international normalized ratio (INR), 1.5. Lactate, full blood count, glucose, creatine kinase, amylase and immunoglobulins were normal. Autoantibodies, serology for hepatitis A, B and C, cytomegalovirus and Epstein–Barr virus DNA and serology were negative. His efavirenz trough level at the time of presentation with jaundice was 2.43 mg/L (therapeutic range 1.0–4.0 mg/L). There was no eosinophilia, but his IgE level was significantly elevated at 972 kU/L [nv < 81.0 kU/L]. Antiretroviral medication was stopped, and the patient was referred to our tertiary paediatric liver centre.

Six days after admission, he was transferred to the paediatric intensive care unit (PICU) because of worsening liver function (INR 4.17) and hepatic encephalopathy. Four days later, he had his first liver transplantation followed by the second within 19 days because of histological features of chronic rejection and severe liver dysfunction. The patient’s progress was complicated by antirejection-drug-related renal dysfunction, hyperlipidaemia and hypertension, as well as critical illness myopathy and cachexia. LFTs were deranged with four allograft biopsies showing features of chronic rejection and hepatocellular cholestasis.

Histology of the explanted native liver showed severe hepatitis with multilacinar parenchymal cell necrosis; no signs of mitochondrial toxicity or excessive copper deposition were seen. Having excluded all of the common causes of ALF, it is possible that severe liver injury in our patient was related to antiretroviral treatment. At the time of his presentation, he had a significantly elevated IgE, which is common in toxic drug reactions. NRTIs are unlikely to be involved as there was no elevated lactate or evidence of mitochondrial toxicity on liver histology. Efavirenz, however, may be implicated. Efavirenz Cmin > 2.18 mg/L during the treatment induction phase has been reported to be associated with increased liver enzymes.3 In our case, the efavirenz level was not measured in the induction phase, but the LFTs were normal at 2 weeks of treatment. The LFTs became severely deranged 13 weeks after efavirenz was started when the trough level of efavirenz was 2.43 mg/L.

Interestingly, after liver transplantation, our patient’s HIV VL remained low without antiretroviral treatment at around 40–500 copies/mL and CD4 count > 200 cells/mm³. However, 6 months after the second liver transplantation, his VL increased to 104 859 copies/mL and the CD4 count started declining. Coincidentally, his liver function deteriorated. The contribution of reactivation of his HIV infection to the deteriorating liver function could not be excluded, and he was started on lamivudine, zidovudine and raltegravir. His antirejection treatment at that time was sirolimus, mycophenolate mofetil and prednisolone. VL became undetectable within 2 weeks, and the CD4 count remained around 500 cells/mm³. The child was discharged home 3 weeks after starting the new antiretroviral treatment. As of January 2009, he is doing well, but his LFTs remain deranged due to mild graft dysfunction.

Choosing treatment for HIV-positive patients after liver transplantation is difficult. There are significant PI and NNRTI interactions with immunosuppressants because of the common cytochrome P450-3A4 isoenzyme pathway; NNRTIs can cause significant liver toxicity and tacrolimus-related renal impairment is a frequent complication in post-transplant patients. We chose two NRTIs and raltegravir. Raltegravir is an integrase inhibitor, which is metabolized in the liver via glucuronidation and not by cytochrome P450-3A4 and has no interaction with immunosuppressant metabolism.4 Its use in post-liver-transplantation adult patients in combination with sirolimus has been reported.5 In our complex paediatric case, ART based on raltegravir has proven to be a safe and effective option, suggesting that it should be considered in paediatric HIV patients after liver transplantation when the choice of antiretrovirals is limited.

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Retrospective evaluation of amphotericin B deoxycholate toxicity in a single centre series of haematopoietic stem cell transplantation recipients

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Sir,

The use of amphotericin B deoxycholate as empirical antifungal therapy was mandatory in our institution until 2005; during the previous 10 years, 123 haematopoietic stem cell transplantation (HSCT) recipients (79 males and 44 females; median age 43 years, range 17–66; 74 autologous, 49 allogeneic) had received 0.7 mg/kg starting 5 days after ineffective antibiotic therapy, including 15 mg/kg amikacin as a single daily dose. After antihistamine premedication, amphotericin B deoxycholate was delivered as an 8 h infusion, and each patient received daily intravenous KCl supplementation was 260 mEq (range 40–500) in the amphotericin B deoxycholate group and 80 mEq (range 0–200) in the no amphotericin B deoxycholate group.

Interest in our data is apparently limited by the fact that new drugs have largely replaced amphotericin B deoxycholate in haematological patients, and Cagnoni et al.2 have shown that allogeneic HSCT cannot be considered a suitable indication for empirical amphotericin B deoxycholate antifungal chemotherapy. Nevertheless, even recent reports have indicated that amphotericin B deoxycholate toxicity can be substantially reduced if the drug is administered appropriately, with hydration3,4 and continuous 24 h infusion5,6 being the favoured methods. As these reports also included a minority of HSCT recipients, we decided to review the data concerning our own series. Apart from confirming that amphotericin B deoxycholate causes unacceptable renal toxicity in allogeneic HSCT recipients, we observed adverse results even in autologous HSCT patients, also including frequent and profound hypokalaemia, and a sustained need for intravenous potassium chloride. Bates et al.1 found that the 79 HSCT recipients in their large and heterogeneous series experienced considerably unfavourable outcomes; although they do not give any information about the amphotericin B deoxycholate schedules, their data suggest that amphotericin B deoxycholate toxicity may be less severe in intensive care units or specialized medical wards whose staff are likely to be more trained in administering amphotericin B deoxycholate, thus justifying efforts aimed at minimizing its toxicity. It is worth mentioning that our findings were observed in patients receiving a low dose of amphotericin B deoxycholate over a short period of time, as is usual in the case of empirical therapy. Moreover, renal toxicity occurred, although the volume of intravenous fluid infusions was comparable to or even higher than that allowing amphotericin B deoxycholate to be delivered safely according to Girmenia et al.2 and Oto et al.4 We did not try to administer amphotericin B deoxycholate as a continuous intravenous infusion because of concerns about its activity. Possibly, renal damage has been somewhat overlooked by...