course of empirical antibiotic therapy with vancomycin and levofloxacin.

Due to lack of improvement in symptoms, a repeat MRI was performed at the end of the treatment course, which revealed evidence of persistent active discitis and osteomyelitis. The patient then underwent an open biopsy, and specimens were sent for culture, which were positive for *Torulopsis glabrata*, vancomycin-resistant *Enterococcus faecium* and methicillin-resistant *Staphylococcus aureus* (MRSA). She was started on voriconazole 250 mg twice a day orally and daptomycin 360 mg (6 mg/kg) intravenously as a single daily dose. After 10 days the patient developed generalized muscular weakness progressing to the point where she could not walk or even get out of bed, followed by non-oliguric acute renal failure with a serum creatinine rising to 27 mg/dL from a baseline level of 9 mg/dL. At this time, the serum creatine phosphokinase (CPK) level was checked, which was 21 243 U/L, and was associated with elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), 375 and 219 U/L respectively. Lactate dehydrogenase (LDH) was also elevated at 666 U/L. Urinalysis was positive for red blood cells, haemoglobin and myoglobin. A diagnosis of acute renal failure secondary to daptomycin-induced rhabdomyolysis was made.

Daptomycin was discontinued and the patient was treated with intravenous fluid administration associated with urine alkalinization. This was followed by progressive amelioration of renal function, normalization of CPK and liver function tests, as well as resolution of muscular weakness.

Daptomycin is a novel cyclic lipopeptide antibiotic with rapid bactericidal activity against most Gram-positive organisms including MRSA and vancomycin-resistant enterococci. It is generally well tolerated by most patients. However, as with all new drugs, uncommon adverse events may become apparent during postmarketing surveillance. Skeletal muscle toxicity was recognized in Phase 1 clinical studies. CPK elevations occurred in 2.8% of cases and 0.2% experienced myopathy. In animal studies, the risk of adverse skeletal muscle effects appeared to be closely related to dosing frequency and were minimized by once daily administration of the drug.

Recently, a case of muscle pain and elevation of CPK induced by daptomycin was reported followed by another case in which myopathy was associated with elevation of CPK as well as liver enzymes. In the first case, CPK elevation was moderate and there was no mention of alteration in liver or kidney function. The second patient, who had a history of hepatitis C, presented with high levels of CPK and liver enzymes, but his kidney function remained normal. Our patient presented with high levels of CPK and transaminases as well as progressive non-oliguric acute renal failure. Discontinuation of daptomycin was followed by normalization of CPK, liver enzymes and renal function as well as disappearance of myoglobin and haemoglobin from urine.

To our knowledge, this is the first reported case of acute renal failure secondary to daptomycin-induced rhabdomyolysis. Interestingly, daptomycin was administered as a once daily dose in this case and no other medication known to induce rhabdomyolysis (e.g. statins or fibrates) was concomitantly used. This shows that once daily dosing may not be completely protective and that additive muscular adverse effects of other drugs are not necessary for daptomycin to induce myopathy.

Based on this observation, we recommend close monitoring of symptoms of myopathy in patients treated with daptomycin, along with serial follow-up of serum creatinine. If muscle weakness and/or elevations in the serum creatinine develop, rapid assessment of CPK, liver function tests and also a urinalysis may be helpful in the early diagnosis of renal impairment and its management in these patients.

**Transparency declarations**

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**References**


**Antiretroviral activity and safety of lopinavir/ritonavir in protease inhibitor-experienced HIV-infected children with severe-moderate immunodeficiency**

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Sir,

HIV-infected children have an immature immune system that is unable to control HIV-1 replication efficiently. Furthermore, many children on highly active antiretroviral therapy (HAART) rapidly experience virological failure allowing the appearance of
Figure 1. Summary of viral load and CD4+ count evolution during follow-up. (a) Mean of log_{10} VL (copies/mL) during follow-up. (b) Percentage of HIV-infected children with VL \( \leq 400 \) copies/mL and VL <5000 copies/mL. (c) Kaplan–Meier estimates to achieve VL \( \leq 400 \) copies/mL for the first time and to have a rebound of viral load after achieving VL \( \leq 400 \) copies/mL during follow-up. (d) Mean of %CD4+ during follow-up. (e) Mean of CD4+/mm³ during follow-up. (f) Percentage of HIV-infected children with CD4+ >25% and CD4+ >500/mm³ during follow-up. (g) Kaplan–Meier estimates to achieve CD4+ >25% and CD4+ >500/mm³ for the first time during follow-up.
HIV-1-quasispecies resistant to antiretroviral drugs.\(^2\) Lopinavir/ritonavir is a protease inhibitor (PI) that has shown potent antiretroviral activity in PI-experienced HIV-infected children.\(^3\)–\(^6\)

We carried out a prospective multicentre study for a period of 18 months to study the effectiveness of salvage therapy with lopinavir/ritonavir in 25 children. The study was conducted according to the Declaration of Helsinki and was approved by the Ethics Committee of our hospital, HGU Gregorio Marañón. The inclusion criteria of 25 children were as follows: (i) CD4+ <25% and <500 cells/mm\(^3\); (ii) virological failure to antiretroviral therapy (ART) with a PI and/or a non-nucleoside reverse transcriptase inhibitor (NNRTI); and (iii) viral load (VL) >5000 copies/mL at entry into the study. The study of evaluation, adverse events and dose of lopinavir/ritonavir on children during follow-up were as described previously.\(^2\) Response to therapy was evaluated every 3 months by serial %CD4+, %CD8+ and VL measurements.\(^4\) There was not a uniform approach regarding ART. Instead, each paediatrician administered the appropriate ART regimen and changed the drugs according to his/her interpretation of the children’s data and international guidelines.\(^4\)

All children were heavily pre-treated with HAART [median (range): 41 (14.6–61.6) months, 4 (1–9) ART-protocol switches, and 8 (4–12) drugs prior to lopinavir/ritonavir therapy]. At baseline, 13 (52%) children had prior diagnosis of AIDS and none of the children progressed to AIDS or death during the follow-up period. No child was lost to follow-up. The new drugs in children with salvage therapy (excluding lopinavir) were 8 nucleoside analogues (NRTI), 3 non-nucleoside analogues (NNRTI) and 2 protease inhibitors (PI). The HAART protocols (NRTI+... ) were 16 with lopinavir/ritonavir, 4 with lopinavir/ritonavir+1 PI (saquinavir, amprenavir or nelfinavir), 1 with lopinavir/ritonavir+2 PI (amprenavir+saquinavir) and 4 with lopinavir/ritonavir+1 NNRTI (efavirenz). As assessed through parental report, adherence was deemed to be good by the clinician in the cohort.

At baseline, median (range) age was 10.9 (3.2–17.1) years. Eleven children had CD4+ <15% and median (range) CD4+ was 16% (1–23). The median (range) \(\log_{10}\) VL was 5.17 (4.06–6) copies/mL. Baseline HIV mutations were studied in 21 out of the 25 samples. The median number of PI mutations was 6 (1–10) and the median number of RT mutations was 6 (3–14). All children had mutations associated with PI and 17 children had ≥1 PI mutation and 11 children had ≥26 PI mutations. The list of PI mutations detected were L10F (n = 3), L10I (n = 11), K20M (n = 2), L24I (n = 2), D30N (n = 4), L33F (n = 2), M36I/V (n = 5), M46I (n = 6), M46L (n = 3), I54V (n = 5), L63A/P (n = 15), A71T/V (n = 8), G73S (n = 2), V77I (n = 8), V82A/F (n = 6), I84V (n = 5), N88D (n = 4) and L90M (n = 11).

‘Lopinavir mutation score’ (LMS) and protease-associated mutations (PRAMs) are likely to contribute to the reduced susceptibility to lopinavir, and provide a potential method as a baseline genotype to evaluate the hypotethical virological response to lopinavir/ritonavir.\(^2\) At baseline, the prevalence of LMS was 5 (0–9) and the prevalence of PRAMS was 1 (0–3). However, we did not find an association with virological failure by Cox regression analysis possibly due to the low number of children.

VL decreased quickly and it remained low during the follow-up study (Figure 1a) with a median (range) decrease at month 18 of 1.9 (0.15–4.2) \(\log_{10}\) VL (copies/mL) (\(P < 0.001\)). The percentages of children who achieved a VL <5000 copies/mL and undetectable VL (uVL) ≤400 copies/mL during the follow-up study were 63% and 47%, respectively (Figure 1b), and 17 of 25 children achieved uVL during follow-up (Figure 1c). After achieving uVL, 8 of 17 children had a rebound of VL ≥400 copies/mL (Figure 1c).

Significant increases in CD4+ were observed. The median (range) increase at month 18 was 15 (–3; 44) %CD4+ (\(P < 0.001\)) and 300 (4; 2434) CD4+/mm\(^3\) (\(P = 0.001\)) (Figure 1d and e). Also, 68% of children had CD4+ >500 cells/mm\(^3\) and 58% had CD4+ >25% (Figure 1f). Next, we analysed the CD4+ increase by Kaplan–Meier analysis (Figure 1g). The median time to achieve CD4+ >25% was 12.6 ± 2.6 months and the median time to achieve CD4+ >500 cells/mm\(^3\) was 5.96 ± 1.7 months.

Lopinavir/ritonavir was well tolerated. One child temporarily interrupted their ART due to diarrhoea and vomiting during 2 weeks and lopinavir/ritonavir was reintroduced again. Adverse events during the follow-up study were reported in 15 out of 25 (60%) children. The most frequent events were gastrointestinal, diarrhoea in nine (36%) children and vomiting or nausea in four (16%) children. Diarrhoea was considered of grade 1 or 2.

Cholesterol levels did not vary significantly during the follow-up [195 (131–295) mg/dL versus 181 (131–275) mg/dL]. However, children had an increase in non-fasting triglyceride levels during the follow-up [126 (71–476) mg/dL at baseline versus 187 (67–609) mg/dL at month 18; \(P = 0.022\)]. Moreover, one child had non-fasting triglyceride levels >300 mg/dL and four children had levels >200 mg/dL. There were no increases in the remaining laboratory parameters (haematology markers, alkaline phosphatase, amylase, creatinine, aminotransferases) during the follow-up.

These children had a high number of HIV mutations that might well be the reason for the prior virological failure.\(^8\) During the follow-up study, >45% of children reached uVL (≤400 copies/mL). These results are in agreement with the experience in heavily pre-treated children on salvage HAART with lopinavir/ritonavir,\(^5\)–\(^6\) and may be considered excellent, despite the fact that most drugs used in combination with lopinavir/ritonavir are supposed to have little activity against the resistant viruses. We also observed a significant increase in the percentage of children with immune-compotence (CD4+ >25% or CD4+ >500 cells/mm\(^3\)). Children were already on PI for many months and a further rise in CD4+ count was observed despite lack of complete virological response.

Lopinavir/ritonavir was well tolerated as reported previously,\(^6\) enabling adherence to treatment. The most common drug-related adverse events were of gastrointestinal nature, and the most common laboratory abnormality was lipid elevation. We found that plasma triglycerides were increased but all children were PI-experienced before starting lopinavir/ritonavir regimens. These children could have had increased lipid and cholesterol at entry into the study. The possibility of hypercholesterolaemia in children with other risk factors for cardiovascular diseases should require surveillance during lopinavir/ritonavir therapy.

In conclusion, salvage therapy with lopinavir/ritonavir exhibited safety and tolerability, and it was associated with substantial antiviral activity (~50% of children with VL <400 copies/mL) and immune recovery.

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