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Research Letter

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Identification of a novel and severe pattern of efavirenz drug-induced liver injury in South Africa

Mark W. Sonderup[a], Debbie Maughan[a], Neliswa Gogela[a], Mashiko Setshedi[a], Helen Wainwright[b], Graeme Meintjes[c] and Wendy Spearman[a]

Efavirenz now forms part of many antiretroviral regimens in low and middle-income countries. Efavirenz-related drug-induced liver injury is not well characterized but is thought to occur less frequently than with nevirapine. We describe our observation of three defined clinicopathological patterns of injury, one of which, submassive necrosis, is associated with significant morbidity and mortality. A high baseline $CD4^+$, younger age and possibly female gender, predicts for the injury.

South Africa is the epicentre of the HIV/AIDS pandemic with an estimated 6.4 million people HIV infected of who 3.1 million have initiated antiretroviral therapy (ART) through a national public sector program [1–3].

Three significant guideline changes have impacted on first-line ART. In 2013, $CD4^+$ threshold for ART initiation increased from 200 to 350 cells/μl and, in 2015, to 500 cells/μl. Second, in 2013, efavirenz became the first-line regimen in ART initiation through use of a fixed-dose combination containing efavirenz/emtricitabine/tenofovir [4]. Third, the WHO programmatic advice that efavirenz is well tolerated in pregnancy and woman of childbearing potential [5]. Consequently, fixed-dose combination is now prescribed in all ART-naïve HIV-infected pregnant women advised to start lifelong ART. Several 100 000 people now commence efavirenz-containing first-line ART in South Africa each year.

Using a definition of grade 3/4 liver enzyme elevations, data for non-nucleoside reverse transcriptase inhibitor-related drug-induced liver injury (DILI) reports cumulative incidence rates between 2 and 20% with nevirapine mostly implicated [6,7]. However, a South African study with efavirenz-based ART found a rate of 7.7 episodes of severe hepatotoxicity per 100 person-years [8]. DILI mechanisms for non-nucleoside reverse transcriptase inhibitors suggest hypersensitivity or idiosyncratic host-mediated phenomena, with most data for nevirapine and few data characterising DILI-related to efavirenz [9].

We have previously described several patterns of efavirenz DILI [10]. Retrospectively, and including 29 patients from the previous study, we reviewed patients who met causality criteria based on: a temporal relationship; excluding acute viral hepatitis (including hepatitis E); negative autoantibodies; radiological exclusion of biliary and vascular obstruction; exclusion of alcohol/herbal toxins; observing the effects of drug dechallenge, including cotrimoxazole and efavirenz; and a histological injury pattern compatible with DILI. The retrospective data guided a prospective observational study underway since October 2014 utilizing the *RUCAM* (Roussel Uclaf Causality Assessment Method) causality tool [11,12]. Biopsy was not performed where severe coagulopathy precluded a well tolerated procedure.

We report the findings to date so as to alert clinicians of a novel and severe pattern of DILI that we have identified. Although efavirenz DILI, despite widespread use, is infrequent, it is associated with substantial morbidity and mortality with many affected patients healthy at the time of ART initiation with no prior AIDS-defining illness.

We report 81 patients (50 retrospective and 31 in prospective cohort), median age 34 years, who met criteria for efavirenz DILI. Ethnically, the majority, 86% ($n = 70$) were Black, the remainder mixed ancestry and most, 73% ($n = 59$), female. In the prospective group, 58% ($n = 18$) were pregnant at the time of initiating ART. The median $CD4^+$ nadir in the cohort was 348 cells/μl [interquartile range (IQR) 173–522] with 27% ($n = 22$) having used or were currently using cotrimoxazole prophylaxis with the median duration on ART 20 weeks (IQR 12–24). In contrast to nevirapine DILI, skin involvement was not observed in affected patients. Three were HBsAg positive and HBeAg negative with liver histology reflective of DILI and not hepatitis B. One patient was hepatitis C antibody positive but RNA negative. No patients fulfilled clinical criteria for tuberculous immune reconstitution inflammatory syndrome [13]. Of those biopsied ($n = 73$), three histological injury patterns were observed. First ($n = 17$), a non-specific hepatitis generally associated with grade 1–2 elevation of serum transaminases (ALT, AST). Second ($n = 20$), a mixed cholestatic-hepatitis associated with grades 2–3 elevation of ALT, AST, alkaline phosphatase and γ-glutamyl transpeptidase and mild/moderate jaundice. Thirdly, submassive necrosis ($n = 36$) with grade 4 elevation of ALT/AST with severe jaundice and coagulopathy (Table 1).

The most severe injury, clinically, biochemically, and histologically, was submassive necrosis characterized by zonal/panzonal necrosis with an 'immuno-allergic'

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Table 1. Laboratory parameters of the three histological patterns of efavirenz-related drug-induced liver injury.

Pattern	Total bilirubin (0–21 μmol/l)	Conjugated bilirubin (0–6 μmol/l)	ALT (5–40 U/l)	AST (5–40 U/l)	ALP (40–120 U/l)	GGT (0–35 U/l)	INR (0.8–1.2)	$^{a}CD_4$ cells/mm^3	HBsAg positive
Submassive necrosis ($n = 36$)	255 (128–337)	173 (83–257)	679 (467–1216)	1038 (612–1825)	215 (156–363)	224 (139–410)	1.68 (1.32–2.33)	508 (335–715)	–
Mixed cholestatis-hepatitis ($n = 20$)	86 (37–206)	52 (20–155)	101 (57–182)	139 (86–395)	379 (193–1048)	609 (500–1232)	1.18 (1.0–1.4)	154 (66–223)	$n = 1$
Nonspecific hepatitis ($n = 17$)	8 (4–24)	5 (1–17)	114 (87–402)	126 (66–473)	210 (131–381)	363 (221–609)	1.11 (1.03–1.20)	159 (30–319)	$n = 2$

Laboratory parameter (laboratory reference range). Data are expressed as median and interquartile range. ALT, alanine aminotransferase; AST aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; INR, international normalized ratio. [a]Nadir CD4 cell count at the initiation of ART.

pattern with inflammatory cell infiltrates composed of lymphocytes, plasma cells, and conspicuous eosinophils. Transaminases at presentation with submassive necrosis were significantly higher (ALT 679 vs. 101 vs. 114 UI/l, $P < 0.0001$) as was jaundice (total bilirubin 232 vs. 86 vs. 8 μmol/l, $P = 0.003$) when compared with the mixed cholestatic-hepatitis and nonspecific hepatitis patterns, respectively. Coagulation abnormalities, measured by the international normalized ratio were significantly greater in the submassive necrosis group compared with the mixed pattern group (1.68 vs. 1.18; $P = 0.0002$).

In univariate analysis, several factors were associated with specific patterns of injury. These included age, female gender, and $CD4^+$ cell count. In a multivariate logistic regression model, submassive necrosis was independently associated with $CD4^+$ cell count of more than 350 cells/μl [odds ratio (OR), 9.4; 95% confidence interval (CI), 2.5–35.8, $P < 0.001$], and female gender (OR, 9.0; 95% CI, 1.4–59.8, $P = 0.023$). Age more than 30 years was protective (OR 0.87; 95% CI, 0.78–0.98, $P = 0.02$). The mixed pattern was associated with a $CD4^+$ of less than 350 cells/μl (OR 11.6; 95% CI, 2.2–61.4, $P < 0.004$) and age more than 30 (OR, 1.1; 95% CI, 1.1–1.2, $P = 0.036$).

The median length of hospital stay was 28 (IQR 11–60) days. Overall, liver-related mortality was 11% ($n = 9$); 6% ($n = 3$) in the retrospective and 19% ($n = 6$) in the prospective cohort, respectively. The majority of deaths invariably occurred within 1 week of presentation. Given the severe immunoallergic injury, we elected to treat submassive necrosis patients with corticosteroids (low-dose 0.25 mg/kg/day prednisone). No apparent excess risk of sepsis has been observed. Resolution is slow, with median biochemical resolution greater than 6 months. Protease inhibitor-based ART has been successfully introduced following resolution.

In summary, we report a case series of 81 patients with efavirenz DILI in a high HIV prevalence and massive increase of efavirenz-based first line ART setting. We observed three patterns of injury, the most severe being submassive necrosis. A high baseline $CD4^+$ seemingly predicts risk for submassive necrosis, with female sex and younger age additional factors. The associated morbidity and mortality is a serious concern. These findings have important implications for developing world ART programs, where millions will be commenced on efavirenz-based ART regimens as criteria for initiation are expanded. Identifying markers that predict for risk of severe efavirenz DILI and developing targeted monitoring strategies (clinical or laboratory) is a research and policy priority.

In the interim, it is important that clinicians are aware of this phenomenon and manage it with rapid cessation of efavirenz when this condition is suspected.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

[a]*Division of Hepatology, Department of Medicine;* [b]*Department of Anatomical Pathology and NHLS; and* [c]*Institute of Infectious Disease and Molecular Medicine and Department of Medicine, University of Cape Town Faculty of Health Sciences and Groote Schuur Hospital, Observatory, Cape Town, South Africa.*

Correspondence to Mark W. Sonderup, Division of Hepatology, Department of Medicine, University of Cape Town Faculty of Health Sciences, Observatory, Cape Town, South Africa, 7925
Tel: +27214066394; fax: +27214044346;
e-mail:msonderup@samedical.co.za

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