

Macroenzyme Creatine Kinase Type 2 accumulation in sera of HIV- infected patients: Significant association with Tenofovir DF (TDF) treatment



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Background

- Macroenzyme creatine kinase (Macro CK) is a diagnostic pitfall in interpretation of elevated serum CK and CK-MB mass concentration and has to be ruled out by electrophoresis.
- Macro CK type 2 (Macro CK2) consists of mitochondrial CK complexes.
- Anecdotal reports demonstrated a strong association of Macro CK2 with malignancy and liver disease.
- Appearance of Macro CK2 is suggested as an indicator of cellular necrosis and cytotoxicity.

Objective

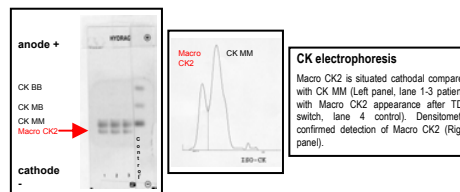
- To evaluate the prevalence of Macro CK2 in HIV infected antiretrovirally treated outpatients.
- To assess possible associations with laboratory or clinical findings.

Methods

- Retrospective and prospective analysis of sera from 468 HIV infected antiretroviral treated outpatients for CK, CK-MB activity and protein weight, electrophoretical behaviour, glomerular filtration rate (GFR), AST, ALT and β -2-Microglobulin levels, CD4+ cell count and HIV-1 viral load.
- Correlation of laboratory findings with clinical data. Student's t test or Mann-Whitney U-test were performed for group analysis.

Results

- In the retrospective analysis CK-MB isoenzyme activity and mass concentration revealed presence of Macro CK2 in 32/408 (7.8%) patients:
- Tenofovir disoproxil fumarate (TDF) containing treatment was the sole common clinical feature.
- Representative laboratory findings suggestive for Macro CK2 were:
 - Total CK activity 249 ± 156 U/l (Ref. <180),
 - CK-MB activity 95 ± 70 U/l (Ref. <15),
 - CK-MB mass concentration 3.0 ± 1.1 ng/ml (Ref. <5),
 - Troponin T negative (Ref. <0.1ng/ml).
- Electrophoresis demonstrated an atypical band migrating cathodal to the CK MM band, consistent with significant Macro CK 2 activity.



- Prospective examination of sera from 41 patients collected prior and past TDF exposure and control sera of 19 different antiretrovirally treated patients detected Macro CK2 in 20 of the 41 (48%) TDF treated patients.
- Macro CK2 appeared at 3 ± 2 months after TDF exposition.
- Macro CK2 persisted for more than 6 months and disappeared after TDF discontinuation.
- In none of these a Macro CK2 was present before TDF exposure. Control sera exhibited no Macro CK2.

Patients with detectable Macro CK2 compared to TDF treated patients without Macro CK2 appearance showed

- a significant induction of serum β 2-Microglobulin levels (2.00 ± 0.66 mg/l vs. 1.77 ± 0.45 mg/l, $p = 0.039$)
- a significant decrease in CD4+ cell count at 3 months (391 ± 196 vs. 544 ± 287 , $p = 0.028$) and at 6 months (397 ± 189 vs. 548 ± 266 , $p = 0.029$) after switch.
- a stringent association with a history of HBV (70% vs. 38%) and HCV (20% vs. 0%) coinfection

GFR and AST to ALT ratio did not differ between both groups.

Conclusions

- Macro CK2 in antiretrovirally treated HIV infected patients pinpoints a strong association with a TDF containing regimen.
- Clinicians should be reminded of the possibility of Macro CK2 appearance in TDF treated patients when results of blood testing lead to suspicion of ischemic or muscular disease.
- Appearance of Macro CK2 after TDF switch is most frequent in patients with a history of HBV or HCV coinfection and is associated with a decrease in CD4+ cell count.
- Accumulation of Macro CK2 could be the result of a direct cytotoxic effect or insufficient Macro CK2 clearance capacity mediated by TDF.