Early ART after Cryptococcal Meningitis Increases Cerebrospinal Fluid Macrophage Activation and Aberrant Th2 Responses in a Multisite Randomized Trial

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Background: In the Cryptococcal Optimal ART Timing (COAT) trial early ART initiation (7-13 days) after cryptococcal meningitis (CM) was associated with higher mortality compared with deferred (5 weeks) ART initiation. Most deaths in the early arm were within 1 month of ART initiation (33/40; primarily related to initial CM). We hypothesized that early ART may lead to rapid changes in immune response within the CNS, contributing to increased death even without overt CM-IRIS.

Methods: 177 COAT subjects were randomized in Kampala and Mbarara, Uganda, and Cape Town, South Africa. Cerebrospinal fluid (CSF) was collected at CM diagnosis (day 0 of amphotericin), randomization (day 8), and day 14. Available cryopreserved CSF was measured by Luminex/ELISA for 19 cytokines/chemokines and 3 soluble markers of macrophage activation. CSF white blood cells (WBC) were measured at the same study time points (n = 167, 138, 120, respectively). Comparisons are by randomized arm (early vs deferred ART).

Results: At the 3 time points 160, 112, and 86 stored CSF samples were available for biomarker testing. There were no differences between arms at CM diagnosis or randomization. At day 14 of amphotericin (median 6 days of early ART) the CSF WBC distribution was different between arms, with those receiving early ART more likely to have CSF WBC >5/μL (58% vs 40%, $p = 0.047$), but less likely to have detectable interleukin (IL)-1b (46% vs 68%, $p = 0.04$). At day 14, there was also a greater Th2 skew by ratio of interferon-g (IFNγ)-to-IL-13 ($p = 0.02$) and a trend of increased IL-13 ($p = 0.05$) in the early ART arm. Day 14 differences in CSF WBC were predominantly driven by increasing cell counts in those with a paucity of CSF pleocytosis at CM diagnosis, occurring in 42% (10/24) persons with CSF WBC <5/μL at CM diagnosis in the early ART arm but in 0% (0/20) in the deferred arm). Most of the mortality during the trial occurred in Uganda (60 of 68 deaths) and many CSF biomarkers statistically differed between Ugandan and South African subjects. In a subgroup analysis of Ugandan subjects at day 14 the early ART arm had evidence of increased monocyte/macrophage recruitment and activation with higher levels of sCD14 ($p = 0.04$), sCD163 ($p = 0.02$), and chemokine MIP1α ($p = 0.04$). A similar trend towards increased Th2 response was also observed, with higher IL-13 ($p = 0.06$) and Th2 skew in the IFNγ/IL-13 ratio ($p = 0.08$).

Conclusions: Early ART led to detectable increases in CSF cellular infiltrate, soluble markers of macrophage activation, and non-protective Th2 responses.