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Stan Deresinski, Section Editor

In the Literature

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Immune Reconstitution Inflammatory Syndrome (IRIS) in HIV-Infected Patients with Cryptococcal Meningitis

Bicanic T, Meintjes G, Rebe K, et al. Immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis: a prospective study. J Acquir Immune Defic Syndr 2009;51:130–4.

Published studies indicate that between 1 in 3 and 1 in 10 HIV-infected patients receiving treatment for cryptococcal meningitis in whom combination antiretroviral therapy (CART) is initiated develop IRIS and that this occurs after median intervals of 1–10 months. The wide variability reported in published reports may be due, in part, to patient and therapeutic heterogeneity and to the retrospective nature of these studies. Bicanic and colleagues in Cape Town, South Africa, have now prospectively evaluated previously antiretroviral-naive HIV-infected patients, examining the incidence, manifestations, and outcomes of cryptococcal meningitis-associated immune reconstitution inflammatory syndrome. The patients had been enrolled in 2 prospective therapeutic studies, and each received induction therapy with amphotericin B with or without flucytosine for up to 14 days, followed by fluconazole consolidation and maintenance. CART (stavudine, lamivudine, and either nevirapine or efavirenz) was initiated 4 weeks after the start of antifungal therapy.

Patients were observed for 9–14 months. IRIS developed in 11 (17%) of 65 patients after a median interval of 29 days (range, 19–63 days) after the initiation of CART. All patients had headache on presentation with IRIS, but none had an abnormal mental status. Two patients had a VIIth nerve palsy, and 1 of these subsequently developed hemiparesis. Cerebrospinal fluid (CSF) culture results were negative for all patients but 1, from whom *Cryptococcus neoformans* was transiently isolated in small number (435 CFU/mL, a marked reduction from baseline); this isolate had developed resistance to fluconazole.

At the time of IRIS presentation, the median opening pressure was 29 cm H_20 compared to 18.5 cm H_20 at the time of diagnosis of cryptococcal meningitis, but this difference was not statistically significant ($P = .54$). Also not achieving statistical significance was the difference in CSF WBC, although the proportion of neutrophils did increase from a median of 0% to one of 10% ($P < .01$). The concentrations of protein and glucose were each similar at the 2 time points, and there was also no significant differences at the 2 points in CSF concentrations of interferon-γ, tumor necrosis factor–α, or interleukin-6. The median CSF cryptococcal

antigen titer had, however, decreased significantly, from 1:2048 to 1:256; 3 patients had a positive India Ink examination at the time of IRIS. Only 2 patients underwent brain imaging with computed tomography, and 2 of these had cerebral infarcts. Repeated lumbar punctures were performed to reduce intracranial pressure and relieve symptoms with a mean of 3 (range 1–12) being required; 4 patients whose symptoms were unresponsive to this intervention were given prednisolone.

A comparison with the 54 patients who did not develop IRIS found that those with IRIS experienced a greater increase of $CD4^+$ T cell count from baseline (mean changes of 220 and 124 cells/mL, respectively; $P = .01$). Four of 11 patients with IRIS died, as did 14 of 54 patients who did not develop this complication, a difference that was not statistically significant. No factors at presentation were found to be predictive of the development of IRIS.

This prospective study indicates that the development of IRIS in the setting of HIV-infected patients with cryptococcal meningitis occurs in almost 1 in 5 patients after initiation of CART. Although the associated morbidity is considerable, mortality is uncommon. Nonetheless, the occurrence of this complication in association with this and other opportunistic infections has led to discussion regarding the appropriate timing of initiation of CART. This issue was addressed in a recently published clinical trial that found no significant difference in the incidence of IRIS with early (median delay, 12 days) versus deferred (median delay, 45 days) initiation of antiretroviral therapy in patients with a variety of opportunistic infections [1]. Early CART, however, was associated with less frequent progression of AIDS or of occurrence of death [1]. The study, however, was dominated by patients with *Pneumocystis jiroveci* pneumonia, and there was an insufficient number of patients with cryptococcal meningitis to allow a firm conclusion with regard to this particular opportunistic infection. The US Centers for Disease Control and Prevention recommendations do not differ greatly from the conclusion reached as a result of this study in that they state that initiation of CART might be delayed, especially in patients with elevated intracranial pressure, until completion of induction antifungal therapy—generally 14 days [2].

Patients with IRIS in the study by Bicanic and colleagues were predominantly treated by repeated removal of CSF by lumbar puncture to control the elevated intracranial pressure and associated symptoms. The most recent recommendations by the US Centers for Disease Control and Prevention also indicate that both CART and antifungal therapy should be continued [2]. They further state that "short-course glucocorticosteroids are recommended by certain specialists" (p. 50).

References

1. Zolopa AR, Andersen J, Komarow L, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PLoS One **2009**; 4(5):e5575.
2. Centers for Disease Control and Prevention. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents—April 10, 2009. MMWR Recomm Rep **2009**; 58(RR-4):1–216. Available at http://www.cdc.gov/mmwr/PDF/RR/RR5804.pdf.

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