Steroids raise cancer risk in TB-associated HIV

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The addition of steroids to tuberculosis (TB) therapy can offer anti-inflammatory benefit to patients with tuberculous pericarditis, a rare cardiac manifestation of TB.

But when these patients are co-infected with HIV this drug combination could increase the risk of cancer, according to the IMPI trial presented as a Hot Line at ESC Congress 2014 today and published simultaneously in the *New England Journal of Medicine*.

Findings from the study suggest "it may be reasonable to add steroids to regular treatment in TB pericarditis patients who don't have HIV infection, but this strategy should be avoided in HIV infected individuals because of the increased risk of malignancy," said investigator Bongani Mayosi, DPhil from Groote Schuur Hospital and the University of Cape Town, South Africa.

"Until now we have had contrasting evidence about this combination therapy and therefore conflicting recommendations about it. However, IMPI, which is the first multi-national trial of TB pericarditis, and the largest trial of adjunctive corticosteroids in TB- associated HIV, settles the question," said Dr. Mayosi.

The study enrolled 1,400 patients (mean age 38.7 years, 44% female) from 19 hospitals in 8 countries. Most patients (81.9%) had probable TB pericarditis, either with (9.7%) or without (72.2%) proven TB elsewhere in the body, while 17.2% had definite TB pericarditis and 1% had an

alternative diagnosis of pericarditis.

The majority of patients (67.1%) were also HIV positive (according to the World Health Organization the risk of developing TB is estimated to be between 12-20 times greater in people living with -compared to without - HIV), 30.8% of subjects were HIV negative, and 2.1% were of unknown HIV status.

Patients were randomised to 6 weeks of treatment with either corticosteroid therapy (prednisolone, n=706) or placebo (n= 694), given concomitantly with anti-TB treatment and anti-retroviral drugs where needed.

Prednisolone and placebo were supplied as identical tablets (5 mg, 30 mg, and 40 mg) and given at a dosage of 120 mg/day in the first week, followed by 90 mg/day in the second week, 60 mg/day in the third week, 30 mg/day in the fourth week, 15 mg/day in the fifth week, and 5 mg/day in the sixth week.

The primary outcome of the study was a composite that included death, a life-threatening accumulation of fluid around the heart known as cardiac tamponade, or constrictive pericarditis, which is a chronic inflammation of the sac around the heart.

Patients were followed for a median of 600 days, after which the incidence of the primary outcome was not significantly different between the prednisolone and placebo-treated groups (14.33 vs 15.05 per 100 person-years, respectively; HR 0.95; P=0.61).

However, when individual elements of the composite outcome were examined, the researchers found a reduced rate of constrictive pericarditis in prednisolone-treated subjects (2.57 vs 4.74 per 100 person-years, respectively; HR 0.54; P=0.005) and consequently a lower rate of

hospitalisation (13.25 vs 16.72 per 100 person-years, respectively; HR, 0.79; P=0.04).

Other components of the composite were similar in both groups including mortality (10.69 vs 9.09 per 100 person-years, respectively; HR 1.16; P=0.24) and cardiac tamponade (1.9 vs. 2.3 per 100 person-years respectively; HR 0.77; p=0.37).

Dr. Mayosi noted that, contrary to recent claims, the addition of prednisolone to standard therapy did not reduce mortality in either HIV-positive or HIV-negative TB pericarditis.

"A large meta-analysis of studies of steroids in all forms of TB that was published in *Lancet Infectious Disease* in 2013 [*Lancet Infect Dis*. 2013 Mar;13(3):223-37] claimed that the addition of steroids to TB treatment reduced death in all forms of TB. This meta-analysis was based on small studies that were not powered for mortality. There is no evidence in IMPI to support this claim for TB pericarditis.' Dr. Mayosi said.

Secondary outcomes that were examined in the study included the effect of prednisolone treatment on opportunistic infections as well as malignancy.

Opportunistic infections occurred at a similar rate in both groups, aside from an excess in prednisolone-related candidiasis, and malignancies "may have" been slightly increased in prednisolone-treated subjects overall compared to placebo (0.97 vs 0.32 cases per 100 person years, respectively; HR 3.00; P=0.05).

However, there was a clear increase in malignancies among HIV-positive subjects in the prednisolone group compared those treated with placebo (0.64 vs 0.08 per 100 person years respectively; HR 7.98; P=0.02). Across both groups, 70% of the malignancies occurred in the first 3

months of enrolment (12 in prednisolone and 4 in placebo-treated groups).

The increase in HIV-associated malignancies is consistent with the results of two previous studies of HIV-associated TB.

"While previous studies were too small to provide a definitive answer to this question, our study was designed specifically to address this, and provides a definitive answer because of its large size and relatively long follow-up," Dr. Mayosi said.

He added there are several potential mechanisms by which steroids, which are immunosuppressive, could play a causal role in cancer.

"The immune system keeps cancer cells in check to a certain degree, and HIV reduces this protection, which is why HIV-associated cancers occur. Steroids further depress the immune system, thus promoting the occurrence of HIV-associated cancers such as Kaposi sarcoma and non-Hodgkin lymphoma which occurred in this study."

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