MEDIA RELEASE

Steroids Raise Cancer Risk in TB-associated HIV

African-led multi-country study will change the clinical management of patients with TB pericarditis and sets new standards for south-led clinical trials

03 September 2014

BARCELONA, Spain – The addition of steroids to tuberculosis (TB) therapy for HIV-positive patients increases the risk of cancer and should be avoided. However, it can offer anti-inflammatory benefit by reducing fibrosis (also called constriction) in patients with TB infection of the heart (TB pericarditis), a dangerous form of TB. TB pericarditis can cause fluid build-up and compression of the heart, and results in the death of a quarter of patients with the condition.

The result of this study lays to rest uncertainty about the use of steroids in TB pericarditis and highlights the increased risk of cancer when these patients are co-infected with HIV, according to the Investigation of the Management of Pericarditis (IMPI) trial. The finding, coming out of a multi-country study in Africa, will change the clinical management of those with the condition on the continent.

"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 to prevent constriction, but this strategy should be avoided in HIV infected individuals because of the increased risk of malignancy," said lead investigator Professor Bongani Mayosi, Head of Medicine at Groote Schuur Hospital and the University of Cape Town.

"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 corticosteroids in HIV associated TB, settles the question," said Professor Mayosi.

The study, which was presented at the European Society of Cardiology congress (and published simultaneously in the *New England Journal of Medicine*), enrolled 1,400 patients with pericarditis (mean age 38.7 years, 44% female) from 19 hospitals in eight countries in Africa.

The majority of patients (67.1%) were also HIV positive, 30.8% of subjects were HIV negative, and 2.1% were of unknown HIV status. According to the World Health Organisation the risk of developing TB is estimated to be 12-20 times greater in

people living with HIV, compared to those without HIV.

Patients were randomised to six weeks of treatment with either the corticosteroid therapy Prednisolone (706 participants) or the placebo (694) given with anti-TB treatment and anti-retroviral drugs, where needed.

Prednisolone and the placebo were supplied as identical tablets. Patients were followed for an average of 600 days.

The study showed that Prednisolone had no impact on the combined primary outcome - i.e. first occurrence of death, cardiac tamponade or constriction - but that it reduced inflammation and scarring of the heart (i.e., constriction) and resulting hospitalisations.

However, the study also showed that there was a clear increase in cancer among HIV-positive subjects in the Prednisolone group compared with those treated with placebo. Across both groups, 70% of the cancers occurred in the first three months of enrollment (twelve in prednisolone- and four in placebo-treated groups).

The increase in HIV associated cancers 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 it, and provides a reliable answer because of its large size and relatively long follow-up," Prof Mayosi said.

He added that 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."

African-led study with little funding

Prof Mayosi has nothing but praise for key partners and their commitment to the study, which faced many challenges due to lack of initial funding.

"This was an African-led study with little funding initially, yet in this context it set new standards for data quality and completeness of follow-up in large African clinical trials, and challenged the perception that 'Africans can't do it' – despite the challenges we successfully resolved a long-standing uncertainty that now impacts on clinical management!" he exclaims.

Key local partners were UCT, Groote Schuur Hospital, the South African Medical Research Council, the Walter Sisulu University/Nelson Mandela Academic Hospital Mthatha in the Eastern Cape and other South African medical schools, and collaborators from Sierra Leone, Nigeria, Kenya, Uganda, Malawi, Mocambique and Zimbabwe. The key international partner was Professor Salim Yusuf and team from

the Population Health Research Institute at Hamilton Health Sciences and McMaster University in Canada.

SOURCES OF FUNDING:

Supported by grants from the Canadian Institutes of Health Research, CANNeCTIN, the Population Health Research Institute, the South African Medical Research Council, the Lily and Ernst Hausmann Research Trust and Cadila Pharma, India. Cadila Pharma also provided the prednisolone tablets used in the study, and supported distribution of the investigational drugs.

DISCLOSURES:

Prof Mayosi reported no other potential conflicts of interest.

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