Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study:
Major Advance in Identification and Treatment of HIV-1 Tuberculosis Immune Reconstitution Inflammatory Syndrome (TB-IRIS): A Common and Serious Complication of Antiretroviral Therapy

1. Summary of the impact (indicative maximum 100 words)

HIV-1 tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS) is an immune complication of antiretroviral therapy that has vastly increased in frequency in low- and middle-income countries over the last decade. This results from the high tuberculosis rates and the widespread availability of antiretroviral therapy. Mortality from this iatrogenic condition is estimated at 3%. Prior to our work this syndrome was poorly defined and management guidelines anecdotal. We produced the widely accepted and implemented case definition. Imperial also conducted the only randomised controlled trial to date of treatment of this condition. The results are incorporated into international guidelines.

2. Underpinning research (indicative maximum 500 words)

Key Imperial College London researchers:
Professor Robert Wilkinson, Wellcome Trust Senior Fellow and Professor in Infectious Diseases (2004-present)
Dr Graeme Meintjes, Wellcome Trust Fellow and Honorary Clinical Lecturer in Infectious Diseases (2008-present)

Tuberculosis (TB) is the commonest opportunistic disease in HIV-1 infected patients in low- and middle-income countries, and is therefore a common indication for starting antiretroviral therapy (ART). When ART is commenced in patients on TB therapy, an immunopathological reaction, known as paradoxical TB-IRIS, commonly occurs (in 8-54% of TB patients starting ART) resulting in new or recurrent TB signs and symptoms (1). TB-IRIS causes considerable morbidity; with 30% requiring hospitalization in a prospective study we conducted (2).

In 2004, knowledge of the pathogenesis and management of TB-IRIS was essentially non-existent because, at that time, the condition had only been observed in relatively small numbers of patients in specialist centres. In 2006, Professor Wilkinson and colleagues at Imperial led the definition of a consensus clinical case definition of TB-IRIS that has since been four times validated and published in 2008, and has become the reference work on the subject being cited 216 times in 4 years (1). In 2004 we set up prospective and cross-sectional studies of the condition in order to gain better understanding of its cause and its management. Important clinical knowledge gained was that TB-IRIS can also occur in patients with undiagnosed multidrug-resistant TB. Thus antitubercular drug resistance should be excluded in all cases of suspected TB-IRIS (3).

We also reported the largest two series of TB-IRIS affecting the central nervous system (CNS). Paradoxical neurologic TB-IRIS accounts for 12% of paradoxical TB-IRIS cases and 23% of patients died (4). Corticosteroids have been used as adjunctive treatment of pathological reactions in TB for several decades. We performed a randomised controlled trial (the only trial ever to be conducted in this condition) of prednisone for the treatment of paradoxical TB-IRIS that demonstrated that a 4-week course of prednisone reduced days of hospitalisation and outpatient therapeutic procedures (2). There were significantly greater improvements in symptoms, Karnofsky score, and quality of life (MOS-HIV) in the prednisone vs. the placebo arm. Chest radiographs improved significantly more in the prednisone arm. Minor infections on study medication occurred in more participants in prednisone than in the placebo arm but there was no difference in severe infections.

We have recently obtained funding for a further trial of prednisone as a preventative therapy.

During the course of our studies we also found evidence that a cytokine release syndrome contributes to pathology in TB-IRIS. IL-6 and TNF were consistently elevated and decreased in serum during corticosteroid therapy. Specific blockade of these cytokines may be rational approaches to immunomodulation in TB-IRIS, as may use of the antiretroviral class of CCR5 antagonists such as maraviroc. These agents may also reduce recruitment of inflammatory cells to disease sites and we are planning a third trial to investigate this hypothesis.

3. References to the research (indicative maximum of six references)

(1) Meintjes, G., Lawn, S.D., Scano, F., Maartens, G., French, M.A., Worodria, W., Elliott, J.H., Murdoch, D., Wilkinson, R.J., Seyler, C., John, L., van der Loeff, M.S., Reiss, P., Lynen, L., Janoff, E.N., Gilks, C., Colebunders, R. (2008). Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis*, 8 (8), 516-523. DOI. Times cited: 226 (as at 2nd October 2013 on ISI Web of Science). Journal Impact Factor: 17.39

(2) Meintjes, G., Wilkinson, R.J., Morroni, C., Pepper, D.J., Rebe, K., Rangaka, M.X., Oni, T., Maartens, G. (2010). Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS*, 24 (15), 2381-2390. DOI. Times cited: 66 (as at 2nd October 2013 on ISI Web of Science). Journal Impact Factor: 6.24

(3) Meintjes, G., Rangaka, M.X., Maartens, G., Rebe, K., Morroni, C., Pepper, D.J., Wilkinson, K.A., Wilkinson, R.J. (2009). Novel relationship between tuberculosis immune reconstitution inflammatory syndrome and antitubercular drug resistance. *Clin Infect Dis*, 48 (5), 667-676. DOI. Times cited: 42 (as at 2nd October 2013 on ISI Web of Science). Journal Impact Factor: 9.15

(4) Pepper, D.J., Marais, S., Maartens, G., Rebe, K., Morroni, C., Rangaka, M.X., Oni, T., Wilkinson, R.J., Meintjes, G. (2009). Neurologic manifestations of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome: a case series. *Clin Infect Dis*, 48 (11), e96-107. DOI. Times cited: 56 (as at 2nd October 2013 on ISI Web of Science). Journal Impact Factor: 9.15

Key funding:

- Wellcome Trust (2007-2011; £316,717), Principal Investigator (PI) G. Meintjes, Wellcome Trust Research Training Fellowship for Scientists from Developing Countries Clinical, proteomic and genomic characterisation of the immune reconstitution inflammatory syndrome in HIV-associated tuberculosis.
- European and Developing Countries Clinical Trials Partnership (2013-2015; €660,000), Co-PIs G. Meintjes and R. Wilkinson, Preventing tuberculosis-associated immune reconstitution inflammatory syndrome in high-risk patients: a randomised placebo-controlled trial of prednisone.

4. Details of the impact (indicative maximum 750 words)

Impacts include: health and welfare, practitioners and services, public policy and services
Main beneficiaries include: patients, practitioners, British HIV Association, US Department of Health, South African HIV Clinicians Society

Until 2004, the literature on TB-IRIS comprised of case reports and case series as well as cohort studies that reported the incidence and risk factors for the condition. There were anecdotal reports of treatments used and response. Standard case definitions were not used across studies making comparison difficult. In 2011 there were an estimated 1.1 million new cases of HIV-positive new TB cases, 79% of whom were living in Africa. All such persons require combined ART and TB treatment, which means that up to 500,000 persons per annum are at risk of TB-IRIS.

The Imperial group led the development of the first consensus case definitions for TB-IRIS under the auspices of the International Network for the Study of HIV-associated IRIS (INSHI) in 2006.

The main rationale for these case definitions was to promote standardization and comparability of studies investigating TB-IRIS. Since publication, they have been widely implemented in clinical and immunological studies of TB-IRIS, not just in resource poor environments, but as a pragmatic standard around the world. The guidelines have now been validated by four independent studies, all published between 2009 and 2010 [1-4].

The Imperial randomised controlled trial of Prednisone was the first (and remains the only) clinical trial to assess a treatment strategy in any form of IRIS. It demonstrated the benefit of steroids for treatment of TB-IRIS in terms of the combined primary endpoint (which was cumulative number of days of hospitalization and outpatient therapeutic procedures counted as an additional hospital day) as well as more rapid symptom response, improvement in quality of life score, chest radiology score and C-reactive protein in patients who received prednisone compared with those who received placebo. Importantly there was no excess of steroid metabolic side effects or severe infections among those who received steroids.

In 2010, the NIH-CDC-HIVMA/IDSA Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents were updated to include recommendations on the management of patients with TB-IRIS. These recommendations cite the Imperial clinical trial findings [5]. These guidelines are accessed by a very wide audience of practitioners treating HIV-infected patients in the US and globally. The British HIV Association guidelines also acknowledge the Imperial work as the only trials-based evidence available [6] and the Imperial research forms part of South African national guidelines [7].

We have addressed many doctors' forums and medical student lectures in South Africa to discuss TB-IRIS and the results of our research. We have also interacted with the patients' advocacy and treatment literacy organisation TAC (the Treatment Action Campaign), including giving talks on HIV-associated TB to their members of the campaign. These interactions have allowed the Imperial research findings to be translated into clinical practice rapidly as acknowledged by revised South African national, British HIV association and US Department of Health and homeland security guidelines [8-9].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[1] Independent validation of the published case definition:
Manosuthi, W., et al. (2009). Clinical case definition and manifestations of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS*, 23 (18), 2467-2471. DOI.

[2] Independent validation of the published case definition:
Eshun-Wilson, I., et al. (2010). Evaluation of paradoxical TB-associated IRIS with the use of standardized case definitions for resource-limited settings. *J Int Assoc Physicians AIDS Care (Chic)*, 9 (2), 104-108. DOI.

[3] Independent validation of the published case definition:
Haddow, L.J., et al. (2010). Validation of a published case definition for tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS*, 24 (1), 103-108. DOI.

[4] Independent validation of the published case definition:
Sharma, S.K., et al. (2010). A study of TB-associated immune reconstitution inflammatory syndrome using the consensus case-definition. *The Indian Journal of Medical Research*, 131, 804-808.

[5] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. US Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf. Archived on 7th November 2013.

[6] British HIV association guidelines: Pozniak, A.L., *et al*. (2011). British HIV Association guidelines for the treatment of TB/HIV co-infection 2011. *HIV Medicine*, 12 (9), 517-524. http://www.bhiva.org/TB-HIV2011.aspx. Archived on 7th November 2013.

[7] Guidelines for antiretroviral therapy in adults by the Southern African HIV Clinicians Society. South African Journal of HIV Medicine (2012), 13, 114-133.

[8] HIV Clinical Resource. Office of the Medical Director, New York State Department of Health http://www.hivguidelines.org/clinical-guidelines/adults/immune-reconstitution-inflammatory-syndrome-iris-in-hiv-infected-patients/. Archived on 7th November 2013.

[9] http://depts.washington.edu/ghivaids/reslimited/case3/discussion.html. Archived on 7th November 2013.