Screen, educate and treat: managing the challenge of TB

S1 HIV-1 INFECTION OF MACROPHAGES MODULATES HOST RESPONSES TO *MYCOBACTERIUM TUBERCULOSIS* TO CONTRIBUTE TO IMMUNOPATHOGENESIS AND VIRAL PROPAGATION

doi:10.1136/thx.2010.150912.1

¹G S Tomlinson, ²P T G Elkington, ¹M Noursadeghi. ¹University College London, London, UK; ²Imperial College, London, UK

Introduction and Objectives Human immunodeficiency virus (HIV)-1 infection increases the risk of active tuberculosis (TB) by 50-fold. The concurrent HIV and TB pandemics therefore represent a major threat to global health. We study the immunopathogenesis of co-infection with a focus on the role of macrophages. These are sentinel cells of the immune system that orchestrate innate and adaptive immune responses, and within the lung, in particular, can host both *Mycobacterium tuberculosis* (MTb) and productive HIV infection. We tested the hypothesis that HIV infection of macrophages modulates host responses to MTb, and contributes to the pathogenesis of co-infection.

Methods Innate immune responses to MTb were assessed in human macrophages with and without productive HIV-1 infection using genome-wide transcriptional profiling. Array data were validated by quantitative PCR of selected genes and Luminex analysis of cell culture supernatants. ELISA and ELISpot assays were used to assess the effects of co-infection on HIV replication and anti-mycobacterial T cell responses.

Results Major gene expression changes assessed by principle component analysis showed that HIV-infected macrophages exhibited attenuated primary transcriptional responses to MTb, but augmented responses at later time points. In keeping with this assessment, we found that MTb stimulation of macrophages induced early IL10 expression, which was attenuated in HIV co-infected cells, and associated with sustained increased expression of pro-inflammatory mediators at later time points. We confirmed the functional relationship between the IL10 response and consequent homeostatic control of inflammatory responses, by complementing deficient IL10 responses in HIV-infected cells to reverse the pro-inflammatory phenotype. We established that exaggerated inflammatory responses in HIV-infected cells were sustained at 72 h, and likely to affect both HIV replication and consequent anti-mycobacterial immune responses. We show that sustained inflammatory responses to MTb are associated with increased HIV replication and have the capacity to alter T cell responses by increasing Th17 polarisation.

Conclusion HIV-1 infection of macrophages attenuates IL10 responses to MTb, and leads to sustained pro-inflammatory responses that support viral propagation and immunopathogenesis of TB.

S2 MULTI-DRUG RESISTANT TUBERCULOSIS (MDR-TB) TREATMENT IN THE UK: A SURVEY OF INJECTABLE USE AND TOXICITY IN PRACTICE

doi:10.1136/thx.2010.150912.2

¹A Sturdy, ²A Goodman, ³R J José, ⁴A Loyse, ⁵M O'Donoghue, ⁵O M Kon, ⁶M J Dedicoat, ⁴T Harrison, ²L John, ³M Lipman, ⁵G Cooke. ¹Imperial College London, London, UK; ²Northwick Park Hospital, London, UK; ³Royal Free Hospital, London, UK; ⁴St Georges Hospital, London, UK; ⁵St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK; ⁶Heart of England Foundation Trust, Birmingham, UK

Rationale Recent discoveries in human genetics have identified mitochondrial mutations which confer a high risk of sensorineural

deafness in individuals exposed to aminoglycosides. Successful MDR-TB treatment often requires prolonged use of these agents. There are little data from the UK to inform the use of genetic tests within MDR-TB patients. We set out to survey MDR-TB practice in the UK with an emphasis on injectable drug use, ototoxicity and audiological monitoring practice.

Methods Five centres took part in a retrospective study of patients initiating injectable treatment for MDR-TB between 1 January 2004 and 31 December 2009. Data were collected regarding patient characteristics, choice of injectable, methods and frequency of ototoxicity screening and incidence of drug-related complications.

Results Treatment for 50 MDR-TB patients was reviewed. 29/50 (58%) patients received amikacin, 11/50 (22%) capreomycin, 4/50 (8%) streptomycin and 6/50 (12%) more than one injectable. Three centres used amikacin as their preferred injectable, two used capreomycin. Audiological screening for ototoxicity was variable. 21/50 (42%) patients received baseline screening within 2 weeks of starting an injectable. 16/50 (32%) patients went on to have monthly audiograms, with the majority screened more infrequently or if symptoms were reported. 12/50 (24%) patients received no screening at any point. Ototoxicity was defined as a 20 dB loss from baseline on audiogram at one test frequency, or a 10 dB loss at two adjacent frequencies, or in the absence of a baseline result, as two or more frequencies below 20 dB. If no audiograms were available, the definition was symptomatic. 14/50 (28%) of patients experienced ototoxicity, with 9/50 (18%) left with persistent hearing loss. Increased age ($p=0.02$), use of amikacin ($p=0.02$) and decreased renal function on therapy ($p=0.01$) were significantly associated with ototoxicity (see Abstract S2 Table 1). No centre routinely tests for mitochondrial DNA mutations.

Abstract S2 Table 1

	Ototoxicity (%) n = 14	No Ototoxicity (%) n = 36	p-Value univariate
Age (years)	41.3 (SD 14.5)	31.9 (SD 11.2)	0.02
Gender			
Female	4 (28.6)	16 (44.6)	
Male	10 (71.4)	20 (55.6)	0.3
Ethnicity			
Caucasian	4 (28.6)	6 (16.7)	
Asian Indian/Pakistani	2 (14.3)	11 (30.6)	
Asian Chinese	0 (0)	2 (5.6)	
Asian Other	1 (7.1)	5 (13.9)	
Asian African	6 (42.9)	11 (30.6)	
All Other	1 (7.1)	1 (2.8)	0.57
HIV status			
Positive	1 (7.1)	4 (11.1)	
Negative	3 (92.9)	32 (88.9)	0.68
Amikacin at any point			
Yes	13 (92.9)	21 (58.3)	
No	1 (7.1)	15 (41.7)	0.02
Capreomycin at any point			
Yes	2 (14.3)	15 (41.7)	
No	12 (85.7)	21 (58.3)	0.07
Duration of injectable treatment (days)	123.4 (SD 62.1)	115.9 (SD 90.2)	0.77
Total dose of injectable agent (g)	96.3 (SD 54.7)	90.7 (SD 63.1)	0.78
Baseline creatinine ($\mu\text{mol/l}$)	85.9 (SD 52.8)	67.7 (SD 12.9)	0.07
Creatinine increase >44 from baseline at any point			
Yes	5 (35.7)	2 (6.5)	
No	9 (64.3)	29 (93.5)	
Not known	0	5	0.01

Conclusions There is local variation in both choice of injectable agent and in ototoxicity screening practices between the MDR treatment