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Hepatotoxicity and antituberculosis therapy: time to revise UK guidance?

Hepatotoxicity associated with antituberculosis therapy is an important clinical problem. Guidelines recommend baseline liver function tests (LFTs) before commencing treatment. In patients with risk factors for hepatotoxicity (ie, chronic viral hepatitis or liver disease, pregnancy or significant alcohol history) or abnormal baseline LFTs, further monitoring is indicated whilst on treatment.^{1,2} In all other cases repeat liver function testing is reserved for patients developing symptoms suggestive of liver dysfunction (fever, malaise, nausea, vomiting, abdominal pain, jaundice or unexplained fatigue). HIV co-infection is not specifically mentioned within UK guidance. Given increasing national rates of tuberculosis/HIV,³ we assessed how this might impact upon current guidelines.

A retrospective case-note review was undertaken of patients treated for active tuberculosis over a year (1 June 2006–31 May 2007) at our central London hospital. Hepatotoxicity was defined as elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than three times the upper limit of normal (>3ULN).

A total of 103 patients started antituberculosis treatment; 53 were male. The median age was 43 years, with two patients under the age of 16 (range 0–82 years). The population

was ethnically diverse: 24 Asian, 46 Black African, 22 European, 11 other. Seventy-nine percent of patients were tested for hepatitis B (9% were positive), 77% for hepatitis C (9% were positive), 3% were pregnant, 5% had a significant alcohol history and 2% had other chronic liver diseases.

The minimum prevalence of HIV co-infection was 23%: 19 patients were known to be HIV positive at baseline. A further 60/84 (71%) had HIV tests; and five patients were new HIV diagnoses.

Seven patients (four of whom were HIV co-infected) with ALT/AST >3ULN at baseline and two patients with no LFTs performed were excluded from analysis. In the remaining 94 subjects, the incidence of hepatotoxicity was 15% (14/94). Of these 57% (8/14) had symptoms consistent with hepatotoxicity, indicating the need for LFT testing; however, 21% (3/14) were asymptomatic. For the remainder, data on symptoms were not clearly available. Ten percent (9/94) developed ALT/AST >5ULN (here, 67% of patients were symptomatic, 11% asymptomatic, 22% symptom data not available). The median time to first abnormal and highest ALT/AST was 6.5 days (range 2–18 days) and 29.5 days (range 7–176 days), respectively. There was a significant difference in hepatotoxicity between HIV-positive and HIV-negative populations: 7/20 (35%) vs 4/55 (7%), respectively ($p = 0.006$, Fisher's exact test). Concurrent use of antiretroviral therapy did not increase the risk in the former ($p = 0.11$, Fisher's exact test) (fig 1).

In 51 patients with normal baseline LFTs and no risk factors for hepatotoxicity, the incidence of hepatotoxicity was 10% (5/51). When HIV-positive individuals were excluded, this fell to 2% (1/44). Furthermore, all three subjects who were asymptomatic at the time of their rise in ALT/AST were HIV co-infected.

In conclusion, most cases of hepatotoxicity continue to be identified by current guidelines, although HIV co-infection does appear to impact upon both the incidence of hepatotoxicity and the use of the recommended algorithm (where LFT monitoring on treatment is indicated according to symptoms). The 1998 British Thoracic Society guidance implies that testing for viral hepatitis should be undertaken at tuberculosis diagnosis.² Our results suggest that routine HIV testing would identify patients not only requiring treatment for HIV⁴ but also at risk of hepatotoxicity. Although a small sample size, we believe our findings will be reproducible in other tuberculosis populations, and that this strengthens the argument for HIV testing to be offered universally in this setting; an approach which avoids "risk assessment" for

Figure 1 Tuberculosis/HIV co-infected patients (with normal baseline liver function tests). Comparison of antiretroviral (ARV) use in hepatotoxic and non-hepatotoxic populations.

HIV, which in itself can generate anxiety and stigma.⁵

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