LETTERS

Factors influencing delay in initiating antiretroviral therapy among HIV infected patients coinfected with tuberculosis

The optimum time to start antiretroviral therapy (ART) in a HIV infected patient receiving antituberculosis therapy (ATT) is unknown. Concurrent treatment of tuberculosis (TB) and HIV is complicated by poor adherence from high pill burden, overlapping toxicities, pharmacokinetic drug–drug interactions and risk of immune reconstitution inflammatory syndrome (IRIS). The risk of disease progression if ART is delayed has to be balanced against the risk of needing to discontinue treatment if ART is started soon. Ninety-seven ART naïve patients were identified (see web repository online for details of patients). Fourteen of 97 patients were lost to our service before they were eligible to start ART; according to BHIVA guidelines, six unexpectedly transferred care to another centre, five were lost to follow-up, two died and one was dispersed to another area. Initiation of ART was within the guidelines in 20/83 (24%) of the remaining patients. Prior to the introduction of the guidelines, ART was delayed in 41/63 (65%) and in 22/34 (64.7%) subsequently (table 1). Two patients had IRIS; both had CD4 <100/µl, neither delayed ART initiation. Four patients died; no deaths could be attributed to delay in initiating ART.

Reasons for delayed ART initiation varied according to CD4 group. In patients with CD4 <100 cells/µl, ART toxicity and TB induced multiorgan failure were common reasons. In this situation it may be unsafe to start ART and delay was appropriate. Among patients with CD4 >200 cells/µl, reasons for delay were often non-clinical. ART was commonly not considered as CD4 counts were high. Many patients declined ART among all CD4 groups, accounting for 21% of delay overall. Crucially, delays in ART initiation did not impact on adverse clinical outcomes and mortality rates were low at 4.8% (95% confidence interval (CI) 1.3% to 11.9%), lower than reported in a retrospective UK multicentre study (3.5%, 95% CI 4.9% to 15.5%) and by Lawn et al from South Africa (10%, 95% CI 5.8% to 18.7%). Rates of IRIS in our retrospective study were low compared with other studies; this may be a result of under-reporting of mild cases. In this specialist HIV/TB treatment centre, there were often cogent barriers to ART initiation; however, the resultant delay did not adversely affect outcomes. Randomised controlled trials are needed, in both developed and resource poor environments, to determine the optimal timing of ART initiation in patients on ATT.

<table>
<thead>
<tr>
<th>Table 1 Reasons for delay in starting antiretroviral therapy in 97 ART naïve HIV infected patients</th>
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<tbody>
<tr>
<td><strong>Patient determined reasons</strong></td>
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<tr>
<td>Patient declined ART</td>
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<tr>
<td>Fear of side effects from ART</td>
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<tr>
<td>Chaotic clinic attendance/poor adherence with ATT</td>
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<td><strong>Physician determined reasons</strong></td>
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<td>Grade III/IV ADR to ATT</td>
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<td>Fear of toxicity/IRIS</td>
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<td>Good CD4, ART not considered by physician</td>
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<td>Intercurrent AIDS defining illness</td>
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<tr>
<td>Prolonged initiation phase of ATT</td>
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<tr>
<td>Other</td>
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<tr>
<td>Non-clinically-determined reasons</td>
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<td><strong>Total</strong></td>
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*Some patients had more than one reason for delay.

ADR, adverse drug reaction; ART, antiretroviral therapy; ATT, antituberculosis therapy; IRIS, immune reconstitution inflammatory syndrome.

REFERENCE

Renal impairment following aminoglycoside therapy in cystic fibrosis

Cystic fibrosis (CF) is a chronic respiratory, life limiting illness in the Caucasian population. Chronic infection with *Pseudomonas aeruginosa* occurs in more than 80% of adults and this contributes to deterioration in lung function over time. A reported long term complication includes renal impairment from presumed cumulative aminoglycoside antibiotics. Aminoglycosides are highly effective against *Pseudomonas aeruginosa* and effectively penetrate the sputum of patients with CF, achieving more effective bacterial killing. The nephrotoxicity of aminoglycosides is reported to be caused by proximal tubular alteration of cell function and cell necrosis.

The study by Smyth et al demonstrates increased renal toxicity measured by plasma creatinine following a case controlled analysis of patients undergoing gentamicin therapy for the treatment of cystic fibrosis exacerbation. The authors did not specify the timing of plasma creatinine measurements in relation to gentamicin dosing (ie, was it collected before the gentamicin dose was given or at an interval following the dose). This would have been important to clarify whether renal impairment was present prior to dosing or occurred subsequently. Of further interest is the measurement of creatinine levels following cessation of gentamicin to elucidate whether renal impairment was persistent or documented evidence of renal function recovery. Plasma creatinine reflects glomerular function rather than tubular function, which was not measured in this study. Plasma creatinine levels are subject to factors such as dehydration, nutrition and body size, and may not be a sensitive test in detecting renal impairment until well established disease has occurred.

The challenge in quantifying renal impairment in cystic fibrosis is to describe the site of damage (ie, renal tubules versus renal glomeruli) and manifestations of early injury. Early and more accurate measurements of glomerular filtration rate may be attained by measuring the protein, cystatin C, or by utilising nuclear medical scans which provide validated measures by renal clearance of exogenous filtration markers, most commonly diethylenetriaminepentaacete (DTPA). With regard to tubular injury, excretion of urinary proteins have been proposed as early markers of aminoglycoside induced tubular toxicity. Steinkamp et al demonstrated that acute tubular injury measured by excretion of urinary enzymes achieve almost complete recovery after 4 weeks from cessation of aminoglycosides. Ideally, prospective studies should measure renal function (both glomerular and tubular) in aminoglycoside naïve cystic fibrosis subjects and document early renal changes following aminoglycoside administration in a dose dependent manner.

A Tai

Correspondence to: Dr A Tai, Department of Respiratory Medicine, Royal Children’s Hospital Melbourne, Victoria 3052, Australia; andrew.tai@rch.org.au

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REFERENCES


Authors’ response

We welcome Dr Tai’s comments on our paper. We described a case control study of acute renal failure in cystic fibrosis (CF) and not a study designed to measure the prevalence, severity or risk factors for renal impairment. Patients with acute renal failure (ARF) were reported to us from 20 UK CF centres and clinical data were extracted retrospectively from the case notes. We therefore adopted a pragmatic definition of ARF (raised plasma creatinine for age with or without oliguria). We agree that substantial renal impairment may occur before a rise in creatinine is seen. However, our intention was to investigate those patients with renal failure requiring dialysis (needed in 13/24 cases) or close monitoring of renal function.

In an earlier paper, we have published the maximum plasma creatinine values seen in patients with ARF, recorded after gentamicin, where this was administered (median creatinine 674 mmol/l (range 124–1972)). At follow-up, 22 of 24 patients had made a full recovery, with a normal plasma creatinine. One patient required long term dialysis (biopsy evidence of diabetic nephropathy prior to ARF) and another long term antihypertensive treatment.

The design of this study did not allow us to assess whether renal impairment was present prior to ARF. The prevalence of renal impairment in adults with CF is reported as 31–42% but the prevalence in children is unknown. We agree that a well designed study of the prevalence and risk factors for renal impairment in children with CF would be useful. We suggested measuring GFR, using the chromium 51 ethylene diamine tetra acetate (EDTA) test.

Six patients with ARF in our series had biopsy evidence of acute tubular necrosis and two had hypomagnesaemia, which suggests tubular damage. We have previously shown that there is a smaller elevation in proximal tubular enzymes with once daily tobramycin administration than with traditional three times daily treatment. Measures of proximal tubular impairment could be included in a future study of renal impairment in children with CF.

A Smyth, C Bertenshaw, S Lewis, I Choonara, A Watson

Division of Child Health, University of Nottingham, Nottingham, UK; *Nottingham University Hospitals NHS Trust, Nottingham, UK.* "Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK.

Correspondence to: Dr A Smyth, Clinical Sciences Building, University of Nottingham, Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB, UK; alan.smyth@nottingham.ac.uk

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REFERENCES


Bronchial asthma on Mount Kilimanjaro is not a disadvantage

Every year, an increasing number of people travel to high altitude and travellers with asthma are becoming more common in remote environments. It is well recognised that certain situations at high altitude, such as exercising in cold air, may provoke symptoms. However, the mountain