Letters to the Editor

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Screening for Mycobacterium tuberculosis prior to anti-TNF therapy—an audit of impact of the British Thoracic Society guidelines on rheumatology practice in an area of low Mycobacterium tuberculosis prevalence

Sir, Anti-TNF drugs have revolutionized rheumatology practice. However, a major concern is the propensity for patients taking these drugs to develop reactivation of latent Mycobacterium tuberculosis (MTB) infection. The British Thoracic Society (BTS) has provided guidelines [1] on risk assessment for TB prior to commencing anti-TNF treatment, but how relevant is it in areas of low MTB incidence?

We examined the pre-treatment screening methods adopted at two UK hospitals situated in the East Anglia region, an area of low MTB prevalence, from August 2000 to August 2005 and applied the BTS guidelines retrospectively to patients otherwise screened in order to evaluate whether it would have had an impact on our clinical practice.

Patients with RA prescribed an anti-TNF drug at the Norfolk and Norwich and Ipswich Hospitals NHS Trust were identified from a pre-existing database and case notes reviewed with regards to pre-treatment screening methods employed. This included a detailed clinical history and physical examination, tuberculin skin testing (Heaf test was done at Ipswich only) and a chest radiograph. We also examined in detail the records of patients diagnosed as having latent MTB at the time of screening to see if there were any subsequent cases of active MTB.

Three hundred and thirty-nine patients were screened and 326 were started on anti-TNF therapy (121 etanercept, 46 adalimumab and 159 infliximab), 329 were Caucasian, 1 Asian British, 1 Chinese and 8 did not have their ethnicity recorded. Three hundred and nine patients (91%) were taking additional immunosuppressive medication. Eighty-one (24%) had tuberculin testing done (Ipswich = 78, Norwich = 3), 7 out of 81 tests (8.64%) were found to be Heaf Grade 3-4, 41 of 81 tests (51%) were negative. Six patients (1.7%) had a previous history of MTB or treatment for it, 238 of 339 (92%) had a chest radiograph done prior to treatment and 4 (1.2%) had an abnormal chest radiograph consistent with old MTB.

Fifteen patients out of 339 (4.4%) were referred to a local TB specialist of which 10 (66%) were diagnosed as having latent TB. Six of 10 (60%) patients suspected as having latent TB started isoniazid chemoprophylaxis. Four chose not to have anti-TNF treatment. None of the patients were found to have active MTB at the time of screening and after a median follow-up time of 4.35 yrs no patients have had reactivation of MTB.

When we retrospectively applied screening algorithms provided by BTS guidelines, we would have needed to have done 30 additional tuberculin tests and 26 chest radiographs within a 3-month period of starting anti-TNF. Four additional patients would have needed an MTB specialist opinion which would probably have been unnecessary given the low prevalence of MTB in our population. (The prevalence rate of MTB infection in the east of England in 2006 was 8/100 000 vs 44.8/100 000 in the London region. In the UK, MTB surveillance is done by the Health Protection Agency [2], which provides an annual report on the regional epidemiology of MTB.)

These results indicate that MTB infection is not a clinical problem in our patient population treated with anti-TNF therapy in the East Anglia region, therefore we are of the opinion that adhering to the BTS guidelines may be an unnecessary practice in areas where MTB prevalence is low. This audit highlights the fact that BTS guidelines might need to be modified to take into consideration the regional variation in the MTB prevalence.

Rheumatology key message

- BTS guidelines might need to be modified to take into consideration the regional variation in MTB prevalence.

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The effect of calcium supplementation on serum urate: analysis of a randomized controlled trial

Sir, Observational studies have shown an inverse relationship between ingestion of dairy products and hyperuricaemia/gout [1]. Intervention studies have also shown that ingestion of dairy products has a short-term urate-lowering effect, and that a dairy-free diet leads to increased serum urate concentrations, by a magnitude of ~0.06 mmol/l [2, 3]. Although dairy products are the principal dietary source of calcium, none of these studies have specifically assessed the influence of dietary calcium intake. Previous reports have implicated calcium metabolism in the regulation of serum urate. A short-term study of patients with idiopathic urolithiasis has demonstrated that intravenous calcium chloride increases uric acid excretion [4]. In patients with primary hyperparathyroidism, serum urate concentrations correlate with PTH levels and decrease after parathyroidectomy [5]. Treatment with human recombinant PTH (teriparatide) also increases serum urate in post-menopausal

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women with osteoporosis [6]. We hypothesized that the documented protective effects of dairy ingestion on hyperuricaemia/ gout is due to a urate-lowering effect of oral calcium ingestion.

This was a pre-defined substudy of a 2-yr randomized controlled trial of calcium citrate supplementation in 323 healthy men aged >40 yrs. The methods and results of the primary study have been reported [7]. The study was approved by the local ethics committee, and each subject gave written informed consent. Trial regimens were: placebo before breakfast and calcium 600 mg in the evening (Ca600); calcium 600 mg twice daily (Ca1200); and placebo twice daily. For the serum urate substudy, 50 subjects from each group (placebo, Ca600 and Ca1200) were randomly selected from those men who completed the study. Fasting morning serum urate concentrations were measured at three time points (baseline, 3 months and 24 months), using the Roche-Hitachi Modular P analyser (Basel, Switzerland). Dietary calcium intake was assessed using a food frequency questionnaire.

The primary end-point for the analysis was change in serum urate. The study had 80% power at the 5% significance level to detect differences of at least 0.06 mmol/l between any of the three treatment groups [8]. Data were analysed using a mixed models approach to repeated measures (SAS v9.1, SAS Institute, Cary, NC, USA). A 5% significance level was maintained throughout. The mean (s.d.) baseline serum urate was 0.33 (0.06) mmol/l. There were no significant differences between the three groups with respect to the baseline characteristics including serum urate.

A weak inverse correlation was observed between baseline dietary calcium intake and baseline serum urate (Pearson r = -0.17, P = 0.03). Regression analysis indicated that a difference of calcium intake of 1200 mg/day was associated with a difference in serum urate of 0.022 mmol/l.

Baseline serum urate also correlated with serum PTH (r = 0.29, P = 0.0003) and total body BMD (r = 0.19, P = 0.02), but not with serum-adjusted calcium (r = 0.15, P = 0.078). The association between BMD and urate was not independent of total fat mass. However, the association with serum PTH remained after adjustment for total fat mass (P = 0.007). Step-wise multiple linear regression analysis of all measures significantly associated with baseline serum urate showed that total fat mass, serum PTH and fasting glucose were the only significant independent predictors of serum urate. In this model, 23% of the variability was explained by total fat mass (P < 0.0001), 3.7% by serum PTH (P = 0.007) and 2.0% by fasting glucose (P = 0.046).

Calcium supplementation led to a significant reduction in PTH (P < 0.0001), but did not result in any difference in serum urate following 3 months or 24 months of treatment (P = 0.97) (Fig. 1). There was no relationship between the change in serum urate and the change in serum PTH at 3 or 24 months (P = 0.47).

This study has demonstrated that although serum urate is weakly associated with dietary calcium intake in cross-sectional analysis, intervention with calcium supplementation does not significantly influence serum urate concentrations in healthy middle-aged men. In addition, we have demonstrated a significant relationship between baseline serum PTH and urate concentrations, independent of total fat mass. This finding is consistent with reports implicating PTH in renal uric acid handling [5, 9]. Whether PTH has a direct effect on uric acid excretion is unknown; our finding of significant inhibition of PTH, but not serum urate, following calcium supplementation suggests that modest changes in PTH do not play an important role in the regulation of serum urate concentrations in healthy individuals.

This study demonstrates that the protective effect of dairy products in development of gout is not due to a urate-lowering effect of dietary calcium. One alternative explanation is that dairy products are relatively low in dietary purines, compared with most other protein sources [10]. Milk also contains uricosuric factors, such as orotic acid, which may reduce serum urate by promoting renal uric acid excretion [10]. Alternatively, high consumption of low fat dairy may reflect avoidance of other lifestyle factors that contribute to hyperuricaemia and gout. Further studies to identify the non-calcium factors contributing to the protective effects of dairy products on serum urate and gout risk are now needed.

**Rheumatology key message**

- The protective effect of dairy products in the development of gout is not due to a urate-lowering effect of dietary calcium.

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Assessment of the impact of new UK guidelines on the management of aromatase inhibitor-associated bone loss

Sir. The aromatase inhibitors (AIs) anastrozole, letrozole and exemestane are approved for the adjuvant treatment of post-menopausal early breast cancer [1]. AIs suppress the non-glandular conversion of androgens to oestrogens and significantly reduce the levels of post-menopausal oestrogen [2]. Concerns about the possible adverse effects of lower oestrogen levels on post-menopausal bone health have been supported by the results of clinical trials for all three drugs [3]. There is general consensus that post-menopausal women commenced on AIs should be screened for osteoporosis by dual energy X-ray absorptiometry (DXA) [4] and such practice has been supported by guidelines produced by the American Society of Clinical Oncology (ASCO) [5]. Oral bisphosphonate therapy is thereby recommended for patients on an aromatase inhibitor with a history of hip/spine fragility fracture or a DXA T-score of ≤−2.5. A United Kingdom Expert Group (UKEG) has recently produced alternative guidelines supported by the National Cancer Research Institute Breast Cancer Study group and the National Osteoporosis Society on the evaluation, monitoring and treatment of bone loss in early breast cancer [6]. The UKEG guidelines recommend bisphosphonate therapy for patients on an AI (i) with treatment-induced premature menopause and either a history of vertebral/hip fragility fracture or a T-score ≤−1.0, (ii) ≥75 yrs old and (iii) with at least one clinical risk factor for fracture and (iii) with a T-score of ≤−2.0 for any patient. All patients who are clinically deficient should receive calcium and vitamin D.

We estimated what the impact of the UKEG guidelines would have been using data from a cohort of 272 patients on aromatase inhibitors referred for DXA scanning to the Royal Lancaster Infirmary between March 2006 and September 2007, before these guidelines were published. This cohort represents 6.1% (272/4479) of all referrals during this period from a catchment population of 320000. The mean age of the cohort was 66.3 yrs (s.d. 6.8 yrs). Data on duration of AI therapy were available in 82 patients. Of these, 43 (52.4%) had been on an AI for <6 months. The median duration of AI treatment was 6 months (interquartile range 1–12 months). Of 204 patients, 69 (33.8%) had received prior tamoxifen. Out of 272 patients, 31 (11.2%) had a known fragility fracture, 10 (3.7%) were on a bisphosphonate, 60 (22.1%) were on tamoxifen. Out of 272 patients, 31 (11.2%) had a known fragility fracture, 10 (3.7%) were on a bisphosphonate, 60 (22.1%) were on tamoxifen. Out of 204 patients, 69 (33.8%) had received prior tamoxifen. Out of 272 patients, 31 (11.2%) had a known fragility fracture, 10 (3.7%) were on a bisphosphonate, 60 (22.1%) were on a calcium supplement and 241 (88.6%) were referred for their first DXA scan. T-scores were normal (T-score >−1) in 106 (39%) patients and osteoporotic (T-score ≤−2.5) in 38 (14%). There was no relationship between duration of AI therapy and unadjusted T-scores (Spearman’s ρ = −0.003).

By applying these guidelines, we estimated that 40 (14.7%) and 84 (30.9%) of patients met the criteria requiring treatment in the ASCO and UKEG guidelines, respectively (Table 1). The application of UKEG guidelines would result in 44 additional patients or a 110% increase in the number of patients on AIs in whom bisphosphonate treatment would have been advised. This finding is most marked in patients over 75 yrs old.

We conclude that implementation of the UKEG guidelines will have a significant impact on the workload of bone density units and also the clinical management of patients on AIs which purchasers, osteoporosis and oncology specialists should be aware of and make provision for.

Table 1. Impact of guidelines on number of patients meeting treatment criteria

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>ASCO (%)</th>
<th>UKEG (%)</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45 (n=5)</td>
<td>0 (0)</td>
<td>2 (40)</td>
<td>−</td>
</tr>
<tr>
<td>45–74 (n=212)</td>
<td>26 (12.3)</td>
<td>47 (22.2)</td>
<td>+80.8%</td>
</tr>
<tr>
<td>&gt;75 (n=55)</td>
<td>14 (25.4)</td>
<td>35 (63.6)</td>
<td>+150%</td>
</tr>
<tr>
<td>Any age (n=272)</td>
<td>40 (14.7)</td>
<td>84 (30.9)</td>
<td>+110%</td>
</tr>
</tbody>
</table>

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