CLINICAL AUDIT

Use of amino terminal type III procollagen peptide (P3NP) assay in methotrexate therapy for psoriasis

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Hepatic fibrosis continues to be a risk in patients receiving methotrexate for psoriasis. Measurement of amino terminal levels of type III procollagen (P3NP) has been advocated as an effective non-invasive test for ongoing hepatic fibrogenesis that could avoid liver biopsies. An audit was conducted to assess the practice of P3NP monitoring using guidelines produced by Manchester and whether the agreed levels correlate with histological severity. Sixty five patients with 174 P3NP assays and 30 liver biopsies were reviewed between the years 1999 and 2003. Total number of patient-methotrexate years was 278.9 and the mean cumulative dose of methotrexate received was 2000 (SD 1838) mg. A higher cumulative dose of methotrexate correlated significantly with high mean and maximum P3NP levels. Of the 30 liver biopsies, 26 (86.6%) showed normal histology or mild to moderate steatosis, three had focal fibrosis, and one had early cirrhosis. A median P3NP value of 5.8 μg/l or higher had a stronger correlation with histological severity. It is concluded that P3NP assay is a valuable adjunct to the clinical management of patients receiving long term methotrexate that can avoid or reduce unnecessary liver biopsies.

Methotrexate (MTX) is an effective systemic antipsoriatic agent but needs monitoring as it carries a risk of liver fibrosis. The amino terminal of type III procollagen peptide (P3NP) is an extension peptide that is cleaved and liberated into extracellular fluid and is a serum marker of collagen turnover. Increased levels occur as a consequence of tissue repair and fibrosis that can be used to predict liver damage. The P3NP radioimmunoassay kit uses a ^{125}I labelled P3NP reagent (Orion Diagnostica, Espoo, Finland) and has a reported sensitivity and specificity of 81%, 62% respectively. The concerns of MTX related hepatotoxicity are real, and although this may not be shared to the same extent in related specialties, the need for serial liver biopsies, considered to be the gold standard for monitoring patients for liver fibrosis, has been questioned in studies conducted by Aithal *et al*[1] and by Mitchell *et al*.[2]

METHODS

We have audited the monitoring of the P3NP assay in our department at the University Hospital of Wales, Cardiff. Chalmers *et al*[3] and Maurice *et al*[4] mention that it is more than a decade since P3NP was reported to correlate well with evidence of hepatic fibrosis and managed using the Manchester protocol, UK. The protocol suggested liver biopsy should be considered if: pre-treatment P3NP levels >8 μg/l or an increase of P3NP above normal range (1.7–4.2 μg/l) in at least three samples over a year or increase of P3NP >8.0 μg/l in two consecutive samples. Our study aim was to audit the practice of monitoring hepatotoxicity with serial P3NP estimations and also to correlate the levels with histological severity of liver damage.

RESULTS

Clinical records of 65 patients with moderate to severe psoriasis receiving MTX during 1999–2003 were reviewed. Details of liver biopsy histology, P3NP assays, duration and cumulative dose of MTX therapy, alcohol intake, concomitant drugs, and liver function tests were recorded. All liver biopsies were done using Tru-Cut needle under ultrasound guidance and graded according to the Roenigk classification scale and reported at the department of pathology, University Hospital of Wales. Levels of intact P3NP were determined using UniQ P3NP RIA assay kit produced by Orion Diagnostica. Data were analysed using SPSS 11.0 and statistical significance measured using Fisher's exact coefficient. Sixty five patients with 174 P3NP assays and 30 liver biopsies were recorded. Liver biopsies were performed according to guidelines with three abnormal (>4.2 μg/l) results in 12 months. Total number of MTX years was 278.9 with a follow up period of 1–14 years with a mean duration of 4.3 (SD 3.9) years. Mean cumulative dose of MTX received was 2000 (SD 1838) mg. Patients with high mean P3NP levels (>4.2 μg/l) had received significantly higher cumulative dose (>1.5 g) of MTX ($p = 0.002$). The cumulative dose of MTX had significant correlation with the maximum P3NP levels ($p = 0.03$). Long duration (>3 years) of MTX treatment, irrespective of the cumulative dose, was consistent with high (>4.2 μg/l) mean and maximum P3NP values but did not reach significance ($p = 0.217$, $p = 0.112$ respectively). Fifteen patients had a total of 30 biopsies. Of the 30 liver biopsies, seven biopsies were performed after introduction of P3NP assay in 1999. Twenty six (86.6%) showed normal histology or mild to moderate steatosis, three had focal fibrosis, and one had early cirrhosis (see table 1 for biopsy results). Sixteen P3NP estimations (28%)—that is, value >4.2 μg/l of a total of 58 correlated at some stage with an abnormal liver biopsy. However, the median P3NP of those with abnormal liver histology was higher than other patients (>5.8 μg/l) and had received a higher median cumulative dose of MTX of 4260 mg.

DISCUSSION

Extrapolating the results from patients who had mild increases of P3NP and underwent biopsy, it is unlikely that with normal P3NP levels significant hepatic fibrosis occurs. The numbers of liver biopsies were significantly reduced after introduction of the P3NP assay in 1999. Regular P3NP estimations could replace cumulative dose of MTX as an indicator for liver biopsy, however it is not organ specific and can measure only ongoing fibrogenesis. This audit follows closely with a recent publication by Maurice *et al*[4] who showed that stable biopsy pairs had P3NP values in the range 2.5–6.9 μg/l. The histological findings of mild to moderate steatosis are not specific for MTX toxicity nor does it warrant

Table 1 Patient characteristics with details of P3NP levels, cumulative dose of methotrexate (MTX-cd), and histological findings on patients who underwent liver biopsy. Most (11, 73.3%) of them had either normal biopsy findings or mild to moderate steatosis

Patient	Sex	Age	MTX (y)	MTX-cd (g)	Mean P3NP (μg/l)	Max P3NP (μg/l)	Number of abnormal P3NP values	Liver histology (P3NP correlate)
1	F	70	13.6	6790	3.9	4.6	4	Normal
2	M	58	15.8	6895	5	6	5	Normal
3	M	74	10	4752	4.9	6.4	3	Mild steatosis
4	M	36	1.1	690	5.8	6.4	4	Mild steatosis ×2
5	M	58	13.9	5970	6.4	10	5	Focal fibrosis ×7 (10 μg/l); 1–6 biopsies: mild steatosis
6	F	52	1.8	1305	3.6	4.8	3	Mild steatosis
7	F	46	7.2	3585	5	6.7	5	Mild steatosis
8	F	53	7.6	5310	5.3	6.4	5	Mild steatosis ×2
9	M	50	8.9	5415	5	5.6	3	Mild steatosis ×2
10	M	41	5.2	3650	5	6.2	4	Focal fibrosis (6.2 μg/l)
11	F	63	6	2500	14	15.8	3	Stage 4 early cirrhosis (15.8 μg/l), 5 biopsies; 1–4 moderate steatosis
12	M	55	5.7	2970	6	6.3	4	Mild steatosis
13	M	65	11	1862	4.3	5	3	Mild steatosis ×3*
14	F	73	6.8	2350	6	6.5	3	Moderate steatosis
15	F	72	6.2	4870	5.1	6.0	4	Focal fibrosis

*Patient 13 was the only one who consumed excess alcohol.

any clinical intervention and has been confirmed by Zachariae *et al*[5] and Chalmers *et al*.[3] In conclusion, we feel that P3NP assay is a valuable adjunct to monitoring patients receiving long term methotrexate and potentially dangerous interventions like liver biopsy can be avoided or reduced.

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