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Comment on: Liver fibrosis in patients with psoriasis and psoriatic arthritis on long-term, high cumulative dose methotrexate therapy

Sir, We read with interest the article by Lindsay *et al*. [1] entitled 'Liver fibrosis in patients with psoriasis and psoriatic arthritis on long-term, high cumulative dose methotrexate therapy' published recently in this journal. The authors concluded that measurement of serum type III procollagen peptide (PIIINP) is not useful for monitoring MTX therapy in PsA on the basis of a single assay of PIIINP performed at the time of liver biopsy. We wish to make the following points.

We have previously shown that in psoriatic patients on long-term MTX, a single measurement of PIIINP does not reliably identify those who have fibrosis on liver biopsy. However, if PIIINP is measured serially and is consistently normal, the risk of significant liver fibrosis is minimal and routine liver biopsies are unnecessary [2]. Similar findings have been reported by other groups [3, 4]. It is likely that PIIINP in serum reflects the activity of fibrogenesis at the time of sampling rather than the degree of established fibrosis seen on biopsy [5]. PIIINP should therefore be measured serially to be a valid test, and we recommended measuring it every 3 months in patients on long-term MTX for psoriasis [6]. A recent multicentre audit [7] confirmed the usefulness of PIIINP in psoriatic patients on MTX and showed that patients monitored using serial PIIINP measurement and selective liver biopsy were subjected to 7-fold fewer liver biopsies compared with those managed according to the guidelines of the American Academy of Dermatology [8] without the evidence that important liver toxicity was missed.

Concern about possible hepatotoxicity remains an important issue during treatment of psoriasis with MTX, particularly considering that the drug is commonly continued long-term for many years. The risk of significant liver fibrosis is low [9], but it is vital to identify those few patients in whom this may be developing. Standard liver enzyme tests [7, 10], radionuclide [11] and ultrasound liver scanning [12] have repeatedly been shown not to be sensitive enough to detect MTX-induced hepatic fibrosis, and percutaneous liver biopsy has for many years been considered as the only reliable method for monitoring these patients until the advent of PIIINP as a serological marker of fibrosis. The risk of liver fibrosis has been reported to be three times higher in patients receiving MTX for psoriasis compared with those on MTX for RA [13]. The relative risk in patients receiving MTX for PsA is not known. Nevertheless, it would appear that some monitoring beyond simple liver enzyme tests is required for these patients, particularly in those with additional risk factors for liver disease.

Release of PIIINP into the circulation is not specific to the liver, and raised levels have been demonstrated in various situations where accumulation and/or degradation of type III collagen occur [2, 7, 14]. Levels are high in children and adolescents and in pregnancy as a result of normal growth. Other reported causes of raised PIIINP include myelofibrosis, SSc, breast carcinoma with bony metastases, ovarian carcinoma, bone fractures, burns and myocardial infarction. The physician must therefore always use clinical judgement to interpret the results appropriately.

It is known that some patients with PsA may also have elevated serum PIIINP unrelated to hepatic fibrosis thus making PIIINP less useful for monitoring MTX therapy in these patients compared with psoriatic patients without arthritis. Zachariae *et al*. [15] found raised PIIINP in 22 (38%) of 58 patients with PsA on MTX in the absence of microscopical evidence of liver fibrosis. In their recent paper [1], Lindsay *et al*. reported an elevated PIIINP in 16 (30%) of 54 patients with arthritis. In our group of 40 patients with PsA [7], only 5 (12.5%) required liver biopsy as a result of repeatedly elevated PIIINP levels and almost 90% had normal levels; significantly, one patient in the group with raised PIIINP was found to have fibrosis on liver biopsy, clearly demonstrating the need for effective monitoring of patients with PsA on MTX. Whilst there may inevitably be false positive results in a minority of patients with active arthritis, repeatedly normal PIIINP values provide strong reassurance that ongoing liver fibrosis is not missed.

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