Letters to the Editor

Clinical improvement in psoriatic arthritis symptoms during treatment for infertility with carnitine

Sirs,

A 36-year-old Caucasian man with a strong family history of psoriasis was diagnosed in the Outpatient Department with psoriatic arthritis (PsA). He presented with psoriatic plaques on the scalp, a painful right knee, low back pain and stiffness radiating into the buttocks; the second finger of the left hand had the characteristic "sausage" appearance. Laboratory tests showed an ESR of 31 mm/h, white blood cells (WBC) 9.8 x $10^3/mm^3$, and positive C-reactive protein (CRP). Rheumatoid factor was negative. Radiographs revealed bilateral sacroiliitis. The patient was treated with non-steroidal anti-inflammatory drugs (NSAIDs) which temporarily controlled the inflammation. He returned 18 months later with painful swelling of right knee with effusion and arthralgia in the left shoulder. The knee fluid contained WBC at 8.4 x $10^3/mm^3$ (74% polymorphonuclear leukocytes, 26% mononuclear cells). No crystals were seen. Following a corticosteroid injection into the knee, the symptoms resolved completely. He was next seen 5 months later when he presented with recurrent joint symptoms involving both the right knee and the left temporomandibular joint.

On this occasion the patient mentioned a problem of infertility between himself and his partner of 4 years duration, occurring under conditions of regular sexual intercourse with a gynaecologically normal partner with no apparent female infertility factors. Therefore, sulfasalazine treatment was not started and the patient underwent an andrological evaluation. He showed no signs of endocrinological or genetic diseases, present or past cryptorchidism, genital infections or genital tract obstructions, varicocele or testicular hypotrophy or anti-sperm antibodies. He had mild oligoasthenozoospermia.

With these characteristics he was included in an ongoing, double-blind, cross-over trial of L-carnitine 2 g/day or placebo. The study design was 2 months washout, 2 months therapy/placebo, 2 months washout and 2 months placebo/therapy (1). Data on routine laboratory tests and adverse events were recorded. The patient reported that his knee pain was reduced during only the first therapy/placebo periods, with an immediate recurrence of symptoms during treatment suspension and the second therapy/placebo period. At the end of this clinical trial, we found that the positive result was obtained during the period of L-carnitine treatment. As his semen parameters had also improved, he was included in a further double-blind, randomised trial (2 months washout, 6 months L-carnitine 2g/day + L-acetylcarnitine 1g/day or placebo followed by 2 months follow up). On this occasion the patient reported that not only his knee pain but also the articular swelling completely resolved during the treatment period, which in this case was also shown at the end of the blinded protocol to consist of carnitine therapy. The patient is now undergoing maintenance therapy with L-carnitine/L-acetylcarnitine alone, and is free of all arthritis symptoms. Laboratory data demonstrate a complete normalization of the ESR, CRP, and WBC count.

Different immune mechanisms, infections, and environmental and metabolic factors are implicated in the pathogenesis of PsA (2). Carnitine plays an important role in the production of cellular energy. It is required for the transport of long fatty acid chains across the inner mitochondrial membrane, thus allowing their catabolism by β-oxidation. It also transports shortened acyl-coenzyme A compounds from the peroxisomes to the mitochondria (3). Long fatty acid chains metabolism is also affected by excessive free radical production through lipid peroxidation. Many investigators have proposed that free radical-mediated lipid peroxidation is critically involved in several disease states, including cancer, post-ischemic re-oxygenation injury and rheumatoid arthritis (RA) (4-7). Concerning PsA, some authors have reported an altered red blood cell fatty acid pattern: in particular, they observed a significant increase in palmitic acid and total satured fatty acids, and reductions in linoleic acid, arachidonic acid and total ω-6 polyunsaturated fatty acids (8). A decrease in plasma carnitine and a correlated increase in malondialdehyde (MDA) levels have been reported in patients with RA. Long fatty acid chains are not carried across the mitochondrial membrane and thus accumulate within the cytoplasm as the carnitine concentration decreases. Consequently, the fatty acids are attacked by peroxide agents and MDA levels increase, resulting in high oxygen radical levels (9, 10).

At present, no data about carnitine and MDAare available for other forms of chronic synovitis, such as PsA. However, the marked clinical improvement seen in our patient during carnitine treatment seems to support its possible role in the pathogenic mechanisms underlying chronic rheumatic conditions.

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No role of factor V Leiden and prothrombin G20210A mutations in the pathogenesis of atherosclerosis and arterial thrombosis in SLE

Sirs,

Individuals with SLE are at greater risk of developing atherothrombotic events. The rate of cardiovascular events is explained by disease- and therapy-related risk factors in association with 'classical' risk factors (1-3). We focused on factor V Leiden and prothrombin G20210A mutations in SLE mediated atherothrombosis, as there is limited data on arterial thrombosis and thrombophilic candidate genes in SLE with respect to known risk factors. These genetic

Table I. Association of the investigated risk factors with atherothrombosis in SLE.

Risk factor	SLE cases OR (95%CI)	MI/CVA OR (95%CI)	CHD OR (95%CI)
Sex	5.81 (0.68-42.91)	3.18 (0.28-36.27)	9.92 (1.06-93.23)
Smoking	0.94 (0.43-2.05)	0.73 (0.29-1.87)	1.33 (0.52-3.45)
Obesity	1.16 (0.57-2.32)	1.23 (0.55-2.73)	1.07 (0.44-2.62)
Diabetes mellitus	1.11 (0.44-2.82)	0.69 (0.21-2.28)	1.91 (0.65-5.61)
Hypertension	1.08 (0.54-2.16)	0.54 (0.23-1.27)	2.59 (1.06-6.33)
DLP	1.95 (0.98-3.90)	2.12 (0.96-4.71)	1.73 (0.72-4.16)
Family history	0.79 (0.40-1.58)	0.39 (0.16-0.93)	1.86 (0.77-4.47)
aCL	1.69 (0.85-3.36)	1.65 (0.75-3.64)	1.75 (0.72-4.25)
Factor VLeiden	2.86 (0.56-14.7)	4.24 (0.78-22.9)	1.09 (0.09-12.5)
Prothrombin G20210A	0.59 (0.09-3.64)	N/A	1.48 (0.23-9.38)
Activity	2.12 (1.04-4.32)	2.19 (0.95-5.06)	2.02 (0.80-5.12)

variations influence arterial thrombosis under restrictive circumstances or upon interaction with other factors. The effect of these mutations on the occurrence of myocardial infarction (MI) and cerebrovascular accidents (CVA) is most prominent in women under 45 years of age, which is also the age group at comparatively highest risk for atherothrombotic complications in SLE (2).

The studied cohort comprised 133 Caucasian SLE patients fulfilling the ACR criteria. We investigated 63 SLE controls without clinical signs of atherothrombosis and 70 SLE patients with ischemic vascular disease (SLE cases), who were stratified into patients with MI and/or CVA (41 individuals), and patients with coronary heart disease without overt arterial thrombotic events (CHD group – 29 individuals). All risk factors were determined by standard criteria and definitions. The disease activity was determined by SLEDAI scored by one of the physicians supervising the study at the regular visits.

All identified mutation carriers were heterozygotes. Factor V Leiden was detected in 6 SLE cases and 2 controls (OR 2.86, 95%CI 0.56 – 14.72). Two SLE cases had the prothrombin G20210A mutation compared to 3 controls (OR 0.59, 95%CI 0.1 – 3.64). The prevalence of factor V Leiden was 1/29 in SLE patients with CHD only, 3/23 in SLE cases with MI, 2/21 in patients with CVA, and 2/63 in SLE controls. Prothrombin G20210A mutation was detected only in SLE cases with CHD (2/29) and in SLE controls (3/63).

Using univariate analysis, disease activity and dyslipoproteinemia (DLP) in the SLE cases overall, and hypertension only in CHD patients, conferred an increased risk for atherothrombosis in the investigated SLE cohort (Table I). There was also a higher frequency of aCL in the SLE cases compared to controls (38/70 vs 26/63); however, this was not statistically significant (Table I). Neither of the mutations nor the other risk factors were associated with the increased risk of atherothrombosis. To determine which investigated laboratory variables were most strongly associated with atherothrombosis, multivariate analysis was performed with atherothrombosis as a dependent variable. Stepwise logistic regression indicated that disease activity was the strongest risk factor for developing an atherothrombotic process ($p = 0.013$). Neither factor V Leiden ($p=0.18$), the prothrombin G20210Amutation ($p = 0.56$) nor their combination ($p = 0.307$) conferred an increased risk. No interaction was observed between disease activity and either factor V Leiden or prothrombin gene mutations. No other factor conferred an increased risk individually; however, the effect of disease activity was potentiated by DLP ($p = 0.01$) and sex ($p = 0.004$). This combination (activity + DLP + sex) was the best predictor of atherothrombosis ($p = 0.0033$). None of the investigated mutations potentiated the effect of this combination.

The potentiation of disease activity with DLP is not surprising, as the occurrence of DLP may not only be due to renal involvement or corticosteroid therapy, but also to the disease activity itself (IL-1 and IFN-α levels correlate negatively with lipoprotein lipase activity). The synergic effect further supports the theory of 'vascular injury', as high lipid levels also directly impair endothelial function.

Taken together, this study does not support a role of factor V Leiden and prothrombin G20210A mutations in the pathogenesis of atherosclerosis and arterial thrombosis in SLE, although the power of this observation is low and a larger sample size will be required to draw more definite conclusions. The study also confirms the importance of disease activity and DLP as important risk factors for atherothrombotic complications in SLE.

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