MATTERS ARISING

EULAR recommendations for the management of knee osteoarthritis

I welcome the publication of the EULAR recommendations for the management of knee osteoarthritis by the EULAR Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT).¹ However, it is out of date and has been superseded by other more up to date publications such as the recommendations for the medical management of osteoarthritis of the hip and knee by the American College of Rheumatology (ACR) Subcommittee on Osteoarthritis Guidelines² and another review of the medical management of osteoarthritis.³ The newer COX-2 sparing non-steroidal anti-inflammatory drugs, rofecoxib and celecoxib are not discussed in the EULAR recommendations, but they have been included in the other reviews.^{2,3}

My second criticism of the report is that it contains statements such as "SYSADOA... may possess structure modification properties", which is misleading and may lead to widespread use of these drugs in the absence of good evidence.

Although the *Annals of the Rheumatic Diseases* is the official EULAR journal, EULAR reports should be peer reviewed before publication. The ACR recommendations for the management of osteoarthritis of the hip and knee were only accepted in a revised format.² Two of the authors of the review in the BMJ³ are also coauthors of the EULAR report.

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- 2 Altman RD, Hochberg MC, Moskowitz RW, Schnitzer TJ. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis Rheum* 2000;43:1905-15.
- 3 Walker-Bone K, Javadi K, Arden N, Cooper C. Regular review: medical management of osteoarthritis. *BMJ* 2000;321:936-40.

Authors' reply

We thank Dr Jawad for his interest in the EULAR recommendations.¹ The fact that the literature search ended at December 1998, excluding evidence based discussion of COX-2 inhibitors, is clearly highlighted and discussed in the paper. Unfortunately, a finite end point needs to be set on any thorough evidence based review, and even the ACR document² was of necessity four months out of date by the time it was published. However, the important strengths of the EULAR document compared with the ACR report are:

1 It used a structured evidence based format rather than just consensus statements.

2 It had input from 23 experts from 12 countries, as opposed to four expert Americans.

3 It undertook additional analyses on published trials to calculate effect sizes and numbers needed to treat where sufficient data were available (that is, it provided new data).

4 The search included surgery and treatments such as topical non-steroidal anti-inflammatory drugs, which are not licensed in the USA and which were excluded from the ACR paper.

5 It provided data on the "epidemiology" and quality of clinical trials in knee osteoarthritis (OA) and highlighted important questions that (still in 2001) need to be addressed by future research.

Unlike the review by Walker-Bone and three other coauthors from Southampton,³ the EULAR report encompassed both medical and surgical treatments, and carefully examined the literature in response to specific clinically relevant questions rather than in an attempt to produce a pragmatic algorithm. We also calculated effect sizes rather than estimates of efficacy, and did not extrapolate treatment data for the knee (the site to which most data relate) to other joint sites. The difference in outcome from these two contrasting approaches is shown, for example, by the recommendation in the BMJ report to consider intra-articular steroid injection only if an effusion is present, whereas the EULAR committee concluded there is no clear evidence to justify a knee effusion as a predictor of response to such treatment.

The qualified statement that "SYSADOAs may possess structure modification properties, but more studies, using standardised methodologies are required" was based on available evidence and made without prejudice. To introduce bias by ignoring published reports on such treatments would indeed be misleading and against all the ethos of evidence based practice.

Although this was a paper that was drafted, edited, and remodified by 21 European experts in OA, the manuscript was peer reviewed by two additional referees after its submission to the *Annals*.

The committee are delighted with the growing interest in the management of OA and that three contrasting reviews were published on the topic in 2000. We, of course, realise the current interest in highly selective COX-2 inhibitors. Importantly, however, the three reports fully concur with respect to the important elements of OA management—the non-pharmacological interventions. They also all agree that paracetamol remains the oral analgesic to try first and, if successful, is the preferred long term oral analgesic.

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Coffee consumption, RF, and the risk of RA

We read with interest the paper entitled "Coffee consumption, rheumatoid factor, and the risk of rheumatoid arthritis",¹ in which an association between coffee consumption and the presence of a positive rheumatoid factor (RF) in healthy subjects was reported. The authors also observed an increased risk of developing seropositive rheumatoid arthritis (RA), particularly in people who were lifelong non-smokers and drinking four cups of coffee or more. Cigarette smoking seemed to be the single most important risk factor for the development of a positive RF in healthy subjects and was strongly associated with coffee consumption. In view of this, however, it seems surprising that there is no additive risk noted for the development of seropositive RA in people who were heavy smokers and also habitual coffee drinkers.

We suggest that the observed risk for developing seropositive RA in people who have never smoked and who consume more than four cups of coffee is possibly confounded by exposure to passive cigarette smoke. For example, coffee in Finland is often consumed in coffee houses, which are prone to be particularly smoky environments, and coffee drinkers are likely to mix with other coffee drinkers, who are statistically more likely to be smokers.

The risk observed for developing seropositive RA in this study is modest for subjects smoking fewer than 14 cigarettes a day (relative risk 1.28, CI 0.63 to 2.57). At face value, it would seem unlikely that passive smoking could play a role in the development of seropositive RA. However, a Chinese study noted that active cigarette smoking was a moderate risk factor for nasopharyngeal cancer (NPC) (OR=1.28, 95%CI 1.02 to 1.61). Despite this, it was observed that women who were lifelong non-smokers had a strong and statistically significant positive association between NPC risk and exposure to substantial passive smoke as a child or as an adult.² Interestingly, those with NPC had an increased risk of a family history of NPC compared with controls. Subjects with RA who are lifelong non-smokers would seem to have a greater genetic predisposition to RA, indeed we have found a strikingly high prevalence of a positive family history of RA in a first or second degree relative in these subjects (54%).³ Possibly, in such genetically "predisposed" subjects passive smoke may induce rheumatoid factor production by a mechanism similar to that in people who are active smokers. The presence of a positive RF in a healthy person is important, as this increases the risk sevenfold for the development of seropositive RA.⁴

A second potential mechanism by which passive smoke inhalation might predispose subjects to RA is by changing the local environment of the nasopharynx. Both the pneumococcus and meningococcus bacteria are carried in the nasopharynx and both invasive pneumococcal and meningococcal disease are seen significantly more often in passive

smokers.^{5,6} It is interesting to note that NPC is associated with the Epstein-Barr virus,⁷ one of a number of viruses which have been implicated in the pathogenesis of RA.⁸ Therefore, passive smoke might potentially predispose subjects to RA as a result of changes within the nasopharynx resulting in antigenic stimulus by a virus that triggers RA.

We agree with the authors that new information is urgently needed about any factor associated with the risk of RA. In view of emerging data highlighting smoking as an important environmental risk factor for the development of seropositive RA,^{3,9} and also this study by Heliövaara *et al*, we propose that passive smoking should be considered as a potential candidate factor for the development of RA.

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Authors' reply

It is not easy to measure passive smoking. Nevertheless, determinations of serum cotinine and thiocyanate recommended for the detection of indirect exposure to tobacco smoke have been shown to indicate exposures of recent occurrence.^{1,2}

To test the assumption put forward by Drs Hutchinson and Moots we studied coffee consumption for its associations with serum cotinine and thiocyanate concentrations in a sample of men who had participated in the Mini-Finland Health Survey and served as an age matched control group in a nested case-control study of lung cancer.³ A modification of the Nicotine Metabolite RIA kit method (Diagnostic Products Corporation, Los Angeles, USA) was used to determine serum cotinine concentrations.⁴ Serum thiocyanate was determined by the spectrophotometric ferric nitrate method.⁵ Of the total of 158 men in the sample, 39 reported current smoking, and 10 others had serum cotinine ≥ 200 mg/l or thiocyanate ≥ 20 nmol/l, suggesting direct exposure to tobacco. Exclusion of these men left 109 non-smokers for the final analyses.

No significant association was seen between the number of daily cups of coffee and serum cotinine concentration (age adjusted $r=0.08$, $p=0.38$). Contrary to the assumption of Drs Hutchinson and Moots, there was a negative correlation between serum thiocyanate level and coffee consumption (age adjusted $r=-0.21$, $p=0.03$). The findings are in agreement with our impression that in Finland coffee is not consumed to any greater extent in notably smoky environments. Rather, coffee consumption is confined to breakfast at home and coffee breaks both during working hours and leisure time.

On the basis of these preliminary results it seems unlikely that passive smoking would have correlated strongly enough with coffee consumption to explain the close associations between coffee consumption and the occurrence of rheumatoid factor (RF) and the risk of rheumatoid arthritis (RA) in our study. Nevertheless, our results are far from being conclusive. Whatever the links between coffee consumption, RF, and RA, we agree with Drs Hutchinson and Moots that passive smoking should be considered a potential risk factor for RA.

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LETTERS TO THE EDITOR

Polyarteritis nodosa complicated by thrombotic thrombocytopenic purpura

A 56 year old woman was diagnosed with polyarteritis nodosa (PAN) in June 1998

based on the presence of fibrinoid necrosis and infiltration of polymorphonuclear cells into medium and small sized arteries on a skin biopsy specimen. She presented with erythema on her arms and legs, with fever and body weight loss. Tender masses were palpable on her right abdomen. Small erythematous lesions and livedo reticularis were seen on the arms and legs.

Laboratory investigation on admission disclosed anaemia (haemoglobin 73 g/l) and leucocytosis (22.5×10^9 /l) consisting mainly of neutrophils (85%). Creatinine clearance was 39 ml/min. Serological examination showed raised levels of C reactive protein (88.6 mg/l). Serological tests for syphilis, hepatitis B virus antigen, and antibody for hepatitis C virus were negative. A high titre of myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) (201 EU) was detected in her sera. An abdominal computed tomography scan showed bilateral perirenal haemorrhages.

The patient was treated with 1000 mg of methylprednisolone for three successive days, followed by 500 mg cyclophosphamide intravenously. Plasma exchange was performed, also. Within three days, treatment had reduced the body temperature to normal and lowered the C reactive protein concentration (<10 mg/l).

The patient rapidly developed thrombocytopenia on the fifth day after admission to hospital, and the lowest platelet count was 15.0×10^9 /l on the eighth day after admission. She became unconscious, and showed features of haemolytic anaemia and renal failure. A provisional diagnosis of disseminated intravascular coagulation was made because of thrombocytopenia, a low concentration of fibrinogen (1.6 g/l), and a high fibrinogen and fibrin degradation product level (22.6 μ g/ml). We treated her with nafamostat mesilate (200 mg/day) and infusion of fresh-frozen plasma. This treatment produced a marked increase in fibrinogen concentration but failed to improve the platelet count. Further laboratory tests showed fragmented red blood cells in peripheral blood. A diagnosis of thrombotic thrombocytopenic purpura (TTP) was established based on these findings. The patient was treated with plasma exchange with 2700 ml fresh-frozen plasma.

Within one week of treatment the platelet count returned to normal and consciousness level improved dramatically. However, renal failure was irreversible and she continued to undergo dialysis. Unfortunately, the patient died from haemorrhage from a duodenal ulcer. Necropsy findings included small and medium sized polyarteritis in the kidney, uterus, pulmonary hilum, hepatic hilum,

Figure 1 Necropsy finding of ileum end. Note fibrinoid necrosis of medium sized artery. Haematoxylin and eosin stain. Magnification $\times 400$.