Smoking is associated with early nodular disease in RF-positive RA

Researchers in Sweden have confirmed that ever having smoked is a strong risk factor for the early development of rheumatoid nodules. Their nested, case–control study found that rheumatoid factor (RF)-positive current or former smokers with rheumatoid arthritis (RA) were much more likely to have early nodular disease—a marker of disease severity—compared with patients who had never smoked. No dose-dependent effect of smoking on nodular disease was found, however, which might indicate that smoking has a greater effect on the initiation of nodular disease than on its progression.

Nyhäll-Wåhlin and colleagues recruited 336 patients with newly diagnosed RA, identified from the BARFOT (Better Antirheumatic Pharmacotherapy) register. All had been symptomatic for ≤1 year and had never received disease-modifying antirheumatic drugs, which are known to increase the risk of developing rheumatoid nodules. The 112 case patients had nodular disease at inclusion on the register; the 224 control patients were matched for age, sex and disease duration. Patients' smoking status was recorded in the register; the authors also obtained a more detailed smoking history from 64 case patients and 146 controls, via a questionnaire.

The authors observed that there were more current smokers in the study cohort (33%) than in the general Swedish population (20%). Patients who smoked were more likely to be RF-positive than nonsmokers, although the association of smoking with early nodular disease persisted after controlling for RF. The authors speculate that RF might mediate the effects of smoking on RA.

Original article Nyhäll-Wåhlin B-M *et al.* (2006) Smoking is a strong risk factor for rheumatoid nodules in early rheumatoid arthritis. *Ann Rheum Dis* **65:** 601–606

TNF inhibitors plus cyclophosphamide could increase patients' cancer risk

Tumor necrosis factor (TNF) induces apoptosis in several tumor types. TNF inhibitors have become a mainstay of treatment in many inflammatory conditions, although it has been suggested that these agents could increase patients' risk of developing cancer. To date, these concerns have principally focused on lymphoma; however, Stone *et al*. now report that patients treated with both a TNF inhibitor and cyclophosphamide might have an increased risk of developing solid tumors, beyond the risk attributable to cyclophosphamide alone.

The authors had previously reported that solid tumors developed in six patients assigned to the etanercept arm of the Wegeners' Granulomatosis Etanercept Trial (WGET), in which 180 patients with active Wegener's granumolatosis were randomly allocated to receive either etanercept or placebo, in addition to standard care. All six patients with tumors had also received cyclophosphamide treatment. There were no malignancies among patients in the placebo arm during the trial (median follow-up 27 months).

Subsequently, the authors calculated that 1.92 malignancies would have been expected to occur in the etanercept arm. During the 3-month observation period after the trial ended, a further three patients developed malignancies, two of whom had been treated with a TNF inhibitor. Overall, 8 of 9 patients who developed a tumor had been treated with a TNF inhibitor and cyclophosphamide.

These findings emphasize the importance of long-term follow-up of patients who are treated with TNF inhibitors, say the authors. They speculate that tumors associated with TNF inhibition might develop more rapidly in patients who also receive immunosuppressive therapy.

Original article Stone JH *et al.* (2006) Solid malignancies among patients in the Wegener's granulomatosis etanercept trial. *Arthritis Rheum* **54:** 1608–1618

Lymphoma risk is elevated even in new-onset inflammatory polyarthritis

Lymphoma is more than twice as likely to occur in patients with inflammatory polyarthritis than in the general population, a UK study has shown—supporting previous findings of a causal link between the incidence of inflammatory polyarthritis (which includes rheumatoid arthritis [RA]) and lymphoma. Whether lymphoma develops as a consequence of immunosuppressive treatment, or of the characteristics of RA or

inflammatory polyarthritis, however, remains unclear. So, Franklin *et al.* measured lymphoma risk in an unselected cohort of patients with inflammatory polyarthritis, and evaluated the effects of disease severity and treatment history on this risk.

This prospective, primary-care-based study recruited 2,105 patients enrolled on the Norfolk Arthritis Register (NOAR) between 1990 and 1999, who were recently diagnosed with inflammatory polyarthritis, and had accessible hospital records. During annual follow-up, data on prescription drug use and disease severity were collected.

After a total follow-up of 15,548 person-years, the incidence of lymphoma was 7.07 cases per 10,000 person-years. Lymphoma risk was highest in patients who had ever tested positive for rheumatoid factor, those ever diagnosed with RA, or those who had ever received disease-modifying antirheumatic drugs. Methotrexate use carried the highest risk (~5 times that of the general population), although all these factors were interrelated.

The small number of lymphoma cases, however, meant that the authors could not draw definitive conclusions about the effects of disease severity and drug exposure on lymphoma risk. They highlight the need for appropriate control groups in future studies that explore the effects of antirheumatic drugs on lymphoma risk.

Original article Franklin J *et al.* (2006) Incidence of lymphoma in a large primary care derived cohort of cases of inflammatory polyarthritis. *Ann Rheum Dis* **65:** 617–622

IL4R mutations predict erosive disease in rheumatoid arthritis

Early treatment of inflammation in patients with rheumatoid arthritis (RA) is thought to limit the progression of joint destruction, so prompt identification of patients at risk of developing erosive disease is important. Genome-wide studies have suggested that the interleukin 4 receptor (*IL4R*) gene is associated with susceptibility to and/or progression of disease in RA. Prots *et al.* investigated the influence of two known single nucleotide polymorphisms in *IL4R* (the resulting amino-acid substitutions Ile50Val and Gln551Arg cause functional changes in its product, IL-4R) on RA susceptibility and progression.

This multicenter study enrolled 471 patients with RA and 371 controls. The presence of erosive disease was determined by examination of hand and foot radiographs taken 2 years after disease onset.

Neither mutation was associated with RA susceptibility, but the Ile50Val variant of IL-4R was associated with the development of erosive disease within the first 2 years of the disease (odds ratio 3.86). Two copies of the allele that resulted in the Ile50Val substitution conferred more than twice the risk observed with one copy; the predictive value of a single copy of this allele for the development of early erosive changes in RA was similar to that of existing markers (including rheumatoid factor).

The authors found that the Ile50Val mutation impaired the function of IL-4R, reducing its response to IL-4. They suggest that this impairment could cause an increase in T_H1-mediated effects of IL-4 (at the expense of T_H2-mediated effects), which could, in turn, worsen inflammation and cause rapid joint damage.

Original article Prots I *et al.* (2006) Association of the *IL4R* single-nucleotide polymorphism I50V with rapidly erosive rheumatoid arthritis. *Arthritis Rheum* **54:** 1491–1500

The course of juvenile idiopathic arthritis can be predicted soon after diagnosis

A single-center study by Singh-Grewal and colleagues has confirmed the existence of monophasic, polycyclic, and persistent disease courses in systemic juvenile idiopathic arthritis (JIA). The team also found that early features of JIA can predict both disease course and the time to remission.

They recruited 45 children (19 male) diagnosed with systemic JIA between 1996 and 2000. Mean follow-up was 4.88 years (data from two children who died within 2 years of the study start were included).

The authors retrospectively compared several remission criteria, and found that inactive disease while not receiving medication for 3 months was the most useful definition for determining the disease course of patients with JIA. These remission criteria identified patients with monophasic JIA with 89.7% specificity and 100% sensitivity, despite only requiring disease to be inactive for 3 months. The authors used