development is the attempt towards side effect reduction. Successful examples are comedication with folic acid during methotrexate treatment and of biphosphonate during corticosteroid treatment.

- Target oriented therapies: whereas anti-T cell therapies so far have not been consistently successful, TNF blocking agents have revolutionised treatment of rheumatoid arthritis. These agents work fast and give a good response in over half of the patients. In addition it has been shown that these therapies have the potential of stopping (radiographic) joint damage. From a practical point of view there are at least a few problems: these therapies are rather expensive and long term follow-up data are not yet available. Especially the latter is important, since TNF plays an important role in inflammation and immunity and therefore chronic suppression may also have negative consequences. Furthermore, it is advised that during TNF blocking therapies, doctor and patient should be alert on the presence or development of infectious diseases.

In view of the above considerations, current use of TNF blocking therapies should be restricted to patients with active disease, despite adequate DMARD therapy, including methotrexate. Possible future strategies will be discussed.

SP0112 EXPERIENCES FROM A NATIONAL SURVEILLANCE PROGRAM FOR EFFECTS, SIDE-EFFECTS AND COSTS OF TNF-BLOCKING AGENTS IN SWEDEN

N Feltelius. Division of Clinical Trials, Medical Products Agency, Uppsala, Sweden

10.1136/annrheumdis-2001.50

The introduction of TNF-blockers in rheumatology has focused on the need for new systems for follow-up of new drugs. Many drugs, like the TNF-blockers have new mechanisms of actions and thus unknown side effects. The national influence on the approval of new drugs has decreased with the common European regulatory system. However the economic consequences of these often expensive treatments are to be handled on the national level. Thus for medical as well as economical reasons national efforts to collect information about recently marketed drugs are important.

In a joint project the Swedish Medical Products Agency (MPA) and The Swedish Society for Rheumatology introduced a follow-up system for the new TNF-blockers when used in rheumatoid arthritis. The system was implemented already before marketing. The aim is to elaborate a system for collecting and reporting pharmacotherapy data from all rheumatology units in Sweden to assess safety and efficacy. This is to optimise treatment but also to form the basis for future surveillance programmes for other new drugs.

The study started in early 1999 with a planned 2-year duration. Assessments of patients are scheduled at 0, 3, 6, 12, 18 and 24 months. Patients included are those with active RA who has failed previous DMARD treatment. All patients are treated on a named-patient-basis and are identified by a unique personal number. This system makes possible future cross-linking with other health data bases. Disease activity is measured according to EULAR core set. The concomitant use of DMARDs and other medications is recorded in detail.

Treatment reports have till now been collected from 1280 patients. The overall clinical outcome of etanercept as well as of infliximab treatment is much in line with what has been reported from randomised controlled studies (RCTs). Only a small

number of patients has been followed for over 12 months but efficacy seems sustained also after this time point.

Reporting of adverse events (AEs) is higher in this surveillance study than what can be expected from the regular spontaneous reporting system. In total 425 AEs have been reported in the cohort. Most frequent are injection site reactions and other dermatological manifestations. Among serious adverse events infections were predominant, with cases of septic arthritis and septicaemia reported. The cost for TNF-blocker treatment in Sweden during the year 2000 is 170 million SK. The spending calculated per inhabitant indicate substantial regional differences in prescription. These figures includes treatment of Crohn's disease patients.

The main conclusions from this study are: 1. Results of TNF-blocker treatment from RCTs seem valid also in an everyday clinical setting. 2. Reporting of adverse events can be substantially improved compared to the existing systems. 3. The logistics of reporting was the main problem in establishing the data collecting system. 4. The involvement of the MPA and the Swedish Society for Rheumatology was necessary to implement the system. 5. For the future the establishing of firm and independent systems that can further develop these kind of drug surveillance is highly desirable. In this struggle the participation of all key players regulatory agencies, professional societies, academic institutions and drug companies is necessary.

Metabolic disorders and the musculoskeletal system – Saturday 16 June, 12.00-13.30/ Forum Hall

SP0115 CRYSTALS AND JOINTS

M Doherty. Academic Rheumatology, City Hospital, Nottingham, UK

10.1136/annrheumdis-2001.51

Primary metabolic disease may predispose to the deposition of a variety of crystals in and around joints, most notably calcium pyrophosphate (CPPD) and apatite. Crystal associated musculoskeletal symptoms may be the presentation of such disease. Renal failure additionally predisposes to urate and oxalate crystal deposition. In most disease states the principal mechanisms relate to elevated ionic products.

There is good evidence that hyperparathyroidism, hypomagnesaemia, haemochromatosis and hypophosphatasia predispose to CPPD deposition; data are less convincing for hypothyroidism, Wilson's disease and other putative associations. Clinical features are acute "pseudogout" attacks in association with polyarticular chondrocalcinosis (CC). Haemochromatosis is exceptional in additionally causing structural joint change and chronic symptoms. Patients <55 years presenting with recurrent acute attacks and polyarticular CC should be screened for metabolic disease (minimum = serum ferritin, magnesium, calcium, alkaline phosphatase). Treatment of the primary disease, however, probably little influences the outcome of CPPD and CC. All these diseases increase extracellular pyrophosphate levels; effects on CPPD crystal nucleation and dissolution, however, are also evident. Rare monogenic familial CC may shortly be explained as primary metabolic disorders of pyrophosphate metabolism involving several enzyme systems.

Milder forms of hypophosphatasia may cause calcific periarthritis due to apatite deposition, in association with axial and peripheral ossifying enthesopathy. Hyperparathyroidism (primary, but particularly secondary or tertiary in patients with renal failure) may also cause this. With renal failure crystal deposits may be massive ("tumoral calcinosis") and both form and resolve with treatment over short periods of time. By far the more common consequence of renal failure, however, is urate crystal deposition. This may result in chronic tophaceous gout and acute attacks. Treatment may prove difficult but allopurinol remains the principal agent. Oxalate crystals can deposit in many tissues, including muscles and joints, and possibly cause myalgia and acute inflammatory episodes in chronic dialysis patients.

REFERENCE

- 1 Jones A, *et al.* Diseases associated with CPPD deposition disease. *Semin Arthritis Rheum* 1992;22:188–202

Targets for treatment – Saturday 16 June, 12.00-13.30/South Hall

SP0116 ANGIOGENIC MEDIATORS IN RHEUMATOID ARTHRITIS

A Koch. *Medicine, Northwestern University Medical School, Chicago, USA*

10.1136/annrhumdis-2001.52

Angiogenesis is important in a variety of fibroproliferative diseases including rheumatoid arthritis (RA). There are a number of angiogenic mediators which may play a role in RA including cytokines and growth factors like transforming growth factor-beta and hepatocyte growth factor. Other angiogenic factors include the fibroblast growth factors (bFGF), vascular endothelial growth factor (VEGF), tumour necrosis factor-alpha, and angiopoietin-1.

VEGF has been characterised over the last few years as an endothelial-selective growth factor. In arthritis models, angiogenesis inhibitors have resulted in decreased severity of arthritis and serum VEGF production. In another model, the soluble VEGF receptor flt-1 resulted in reduction of arthritis. These results indicate that modulation of angiogenesis may modulate arthritis, at least in animal models. In human RA, several groups have found VEGF in the joints. Recent interest has focused on VEGF production by RA fibroblasts. In RA patients treated with anti-TNF-alpha, vascular deactivation occurs so that serum levels of VEGF fall along with clinical improvement. Hence, VEGF is likely an important mediator of angiogenesis in the RA joint.

What is the mechanism of action of angiogenic mediators like VEGF and bFGF? Particularly important in mediating angiogenesis are the alpha v beta 3 and alpha v beta 5 integrins. It appears that cytokines like TNF-alpha or bFGF act via alpha v beta 3 integrin while VEGF acts via alpha v beta 5 integrin. In an animal model, inhibition of alpha v beta 3 integrin resulted in amelioration of a model of lapine arthritis.

We have recently examined the role of interleukin (IL)-18 as an angiogenic mediator in RA. We have shown its role in angiogenesis using a number of experimental models. IL-18 mediated endothelial chemotaxis in a modified Boyden chamber assay. IL-18 induced endothelial tube formation on the matrix protein Matrigel. Moreover, IL-18 was angiogenic *in vivo* in rodent Matrigel plug and sponge granuloma assays. IL-18 accounted for a large portion of the chemotactic activity for endothelial cells

found in RA synovial fluids. IL-18 appears to induce angiogenesis via the alpha v beta 3 integrin.

Angiogenic mediators can be broadly divided into two groups, stimulators or proangiogenic factors, and inhibitors or angiostatic factors. The regulation of angiogenesis is likely to result from a delicate balance of angiogenesis inducers and inhibitors.

Some of these inhibitors include interferons alpha, beta, and gamma and interleukin-12, and interleukin-4. Other inhibitors include placental ribonuclease inhibitor, protamine, retinoic acid and tissue inhibitor of metalloproteinase.

We have shown that another cytokine, IL-4, is a potent anti-angiogenic factor. Moreover, when an adenoviral vector bearing the IL-4 gene was given to rats prior to development of adjuvant-induced arthritis, these animals showed less severe arthritis and their joints exhibited decreased inflammatory infiltrate and decreased angiogenesis compared to controls.

Another emerging paradigm is that angiogenesis inhibitors often reside within other proteins. The idea that endothelium is quiescent for long periods of time and yet can be induced to sprout new capillaries in a matter of hours in response to an angiogenic stimulus, suggested that angiogenesis regulators might be stored for expedient use. Examples of this include angiostatin and endostatin.

It is likely that inhibitors of angiogenesis are present in the RA synovium, but are outweighed in effect by angiogenesis inducers.

Can angiogenesis regulation help us in the therapy of patients with RA? There are a number of endogenous and exogenous inhibitors of angiogenesis which have been identified to date. These include a cartilage-derived factor, troponin, angiostatic corticosteroids, minocycline, fumigillin, chloroquine, sulfapyridine, methotrexate, penicillamine and thiol containing compounds such as gold compounds.

Can we use angiogenic markers to help guide our therapy in diseases like RA? Some preliminary data from several centres indicate that VEGF and bFGF are increased in RA vs. normal serum, especially in early erosive RA and in patients who are anti-Sa and anti-native collagen positive. Serum VEGF is increased in early RA. Early RA synovial fluid VEGF and MMP-9 correlate with each other and with arthroscopic synovitis and vascularity scores. Evidence is mounting that markers of angiogenesis may help us in early RA.

Can we use angiogenic markers to predict RA disease outcome? One study presented in abstract form indicated that serum vascular markers predicted disability and radiological changes in RA. Serum VEGF was associated with greater disease activity and soluble selectins were associated with increased disability. Hence, it is tempting to speculate that angiogenic markers may help guide us in RA therapy in the future.

Review session N° 1 – Wednesday 13 June, 14.00-16.00/South Hall

SP0011 OSTEOARTICULAR DISORDERS OF RENAL ORIGIN

T Bardin. *Fédération de Rhumatologie, Lariboisière Hospital, Paris, France*

10.1136/annrhumdis-2001.53

Renal failure is a source of musculoskeletal features, especially in patients treated by maintenance haemodialysis. In these, bone