Pulsed electromagnetic field therapy in the management of knee OA

It seems most unusual that in a review of “all currently available treatments” for knee osteoarthritis (OA) by 21 authorities and “two experts in the field of guidelines methodology”, pulsed electromagnetic field therapy was not mentioned in the text or the 51 references.1 This is particularly troubling because over 2800 publications between 1966 and 1998 were retrieved. An identical search for efficacy of magnetic field therapy during this period listed 51 studies with at least one control group,2 including two double blind trials citing benefits in knee OA from a peer reviewed arthritis journal.3 In 1999 over 50 000 patients received pulsed signal therapy (PST) prescribed by over 1000 doctors at more than 300 clinics and hospitals in 16 countries, where it is usually reimbursed by fiscal intermediaries because of its proven record of cost effectiveness and safety. A summary of PST double blind and randomised study results in over 50 000 patients has been published,4 and findings in 100 000 patients (the vast majority with knee OA) have also been reported at recent international conferences.5 Although “alternative” remedies, ranging from minerals, vitamins, nutritional supplements, and capsaicin and diclofenac gels to sex hormones were discussed, in contrast with PST, none satisfied the category criteria the panel established to determine strong recommendation. Nor do any have the solid basic science studies that PST provides with its in vitro support for mechanisms of action to explain efficacy based on proteoglycan synthesis and chondrocyte regeneration results.*

Pulsed signal therapy is the result of three decades of research designed to characterise the piezoelectric signal that normally stimulates chondrocyte activity by creating a streaming current in the extracellular matrix when bone is subjected to pressure. Although the transmission of this signal is impaired in OA, PST can reproduce this streaming potential in the extracellular matrix and cause cartilage and chondrocyte stimulation studies. The Eleventh International Congress on Stress Abstracts Book, 2000.

Pulsed electromagnetic field therapy, with the benefits described above, is an evidence based alternative option.


Authors’ reply

We thank Dr Pfeiffer for raising this point. The EULAR recommendations for the management of knee osteoarthritis1 combined an evidence based approach and a consensus approach. The evidence based approach—that is, the literature research, was only applied for the treatment modalities selected by the experts at the first meeting of the committee (see table 1 of the paper).

Pulsed electromagnetic field therapy, with other less commonly used interventions, was not included in this list, and its evidence for efficacy was therefore not assessed. However, as emphasised by Dr Pfeiffer, an evidence based evaluation of all other interventions would be of interest and could be considered for inclusion in the next round of evidence based guidelines.


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Caudal epidural injections

Price et al recommend that caudal epidural injections should be carried out with x-ray screening. In practice the technique is often performed in the outpatient clinic, where screening facilities are not usually available.

The major issue raised by Dr Fiehn is that he believes that in patients with APS one should use adjusted, not fixed, doses of LMWH. He believes that in patients with APS one should advise adjusted doses of LMWH in all pregnant patients with APS.

We thank Dr Fiehn for his interest and comments on our recent leader in the Annals. At present, there are insufficient data from randomised trials to give evidence based guidelines for optimal (prophylactic) treatment of many of the clinical manifestations of the antiphospholipid syndrome (APS). This not only holds for prevention of pregnancy related complications, the topic of our leader, but also for treatment of thrombosis related to antiphospholipid antibodies.

The major issue raised by Dr Fiehn is that he believes that in patients with APS one should use adjusted, not fixed, doses of low molecular weight heparin (LMWH). It is well known that anti-Xa activity relates to anti-thrombotic effects of LMWHs, and that the amount of LMWH needed to achieve and maintain a certain range of anti-Xa activity increases during the course of pregnancy. In most patients dose adjustment is needed in the second, and, in some, in the third trimester (mean (SD) 20.5 (8.2) weeks), but individual patients vary widely in the time when the dose of LMWH needs to be adjusted from once to twice daily. Despite this, there is so far no clinical proof that for thromboprophylaxis in pregnancy or prevention of poor pregnancy outcome an adjusted dose LMWH (with cumbersome and costly monitoring of pre- and post-injection anti-Xa activity) is better than a fixed dose based on body weight. Therefore, we do not share Dr Fiehn’s view that one should advise adjusted doses of LMWH in all pregnant patients with APS.
and the IL1ra have co-evolved as a cytokine control mechanism: agents eliciting IL1 production generally induce IL1ra gene transcription as well, either directly or through a feedback loop triggered by IL1 itself. IL1ra competes with IL1 for binding to the cognate receptor, but it produces no known signalling events upon binding. Additionally, one of the two IL1 receptors, type II, also lacks any known signalling capacity and is thought to function as a decoy binding site. If it is assumed that polymorphisms found in various members of the IL1 gene family modify gene function then the implication is that they should be studied collectively, not individually. In support of this argument comes recent experimental evidence showing that individual IL1-ra levels are determined by allelic combinations within the IL1 gene family, as well as evidence for linkage disequilibrium between polymorphic markers spread across the IL1 gene family locus. It is fair to say that Crilly and colleagues did allude in their paper to the possible existence of the interlink 1 (IL1) gene family allele would be useful. However, for a large number of alleles to be tested a considerable sample size would be needed to correct for multiple allele testing. This would require a multicentre study; this is limited by funding constraints.

Secondly, for the statistical analysis we predefined early and late surgery. Analysis was undertaken after discussion with a qualified medical statistician. Should the correspondents wish to analyse our data, we would be happy to allow access if guarantees can be provided.

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Author’s reply
I thank Dr Vamvakopoulos for his interest in our article1 and would like to make the following response.

We agree that testing for haplotype combinations of the interlink 1 (IL1) gene family allele would be useful. However, for a large number of alleles to be tested a considerable sample size would be needed to correct for multiple allele testing. This would require a multicentre study; this is limited by funding constraints.

Secondly, for the statistical analysis we predefined early and late surgery. Analysis was undertaken after discussion with a qualified medical statistician. Should the correspondents wish to analyse our data, we would be happy to allow access if guarantees can be provided.

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LETTERS TO THE EDITOR

A case of shingles mimicking carpal tunnel syndrome

A 59 year old woman with an eight year history of erosive rheumatoid arthritis (RA) receiving sulfasalazine and penicillamine presented with severe sudden onset pain radiating from the left elbow to the left thumb, index and middle fingers. Examination disclosed synovitis of the left wrist, which might have caused median nerve compression. The wrist joint was injected with 20 mg of triamcinolone acetate with 1% lidocaine (lignocaine). She returned the following morning complaining of worsening pain. She was clinically well with no fever. White cell count was normal, but the erythrocyte sedimentation rate (ESR) was raised at 73 mm/1st h. A transcutaneous nerve-stimulating (TENS) machine was applied and she was prescribed amitriptyline 25 mg at night. The following day she had improved significantly but had developed a vesicular rash in the C6 dermatome consistent with herpes zoster infection (fig 1). Viral titres were consistent with current varicella zoster infection.

DISCUSSION
Establishing the cause of pain in patients with RA can be notoriously difficult. In addition to the psychological factors that influence pain perception, wrist and hand pain may result from rheumatoid synovitis, soft tissue inflammation, or mechanical nerve compression at wrist, elbow, and cervical spine. Herpes zoster infection is heralded by burning discomfort in a dermatomal distribution, which may occur for up to 5 days before the onset of the typical rash. Cervical dermatomes are affected in up to 15% of patients and may result in diaphragmatic paralysis and lower motor neurone paresis. In this case the occurrence of prodromal symptoms of herpes zoster mimicked the symptoms of carpal tunnel syndrome, presumed secondary to RA synovitis.

RA increases the risk of herpes zoster infection.1 In one series the use of low dose methotrexate, long duration of disease, and seropositivity were risk factors for subsequent infection.2 Gold treatment may also increase the likelihood of shingles.

Immunocompromised patients should receive acyclovir early to avoid viral dissemination. In patients with RA the complexity of the differential diagnosis may delay diagnosis unless the possibility of herpes zoster infection is kept in mind.

Conflict of interest: none.

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Aza-thioprine hypersensitivity

Systemic hypersensitivity is a rare but documented side effect of aza-thioprine. The common adverse effects of aza-thioprine include

fevers, gastrointestinal disturbances of nausea and vomiting, granulocytopenia, and hepaticcellular injury. More rarely, hypersensitivity can present with features of severe systemic infection and end organ dysfunction.\textsuperscript{2} Azathioprine is a commonly used immunosuppressive drug and is used in many medical specialties. Therefore recognising azathioprine hypersensitivity is important for all doctors. We report a case in which we suspect such an azathioprine hypersensitivity reaction.

A 32 year old Asian woman with mixed connective tissue disorder presented with a one day history of general malaise, fevers, and painful digits. Fourteen days earlier treatment had been started with azathioprine 50 mg daily, and her prednisolone increased from 5 mg to 15 mg daily owing to the development of proteinuria (1.5 g on 24 hour urine collection) and urticarial vasculitis on her lower legs.

On examination she was shocked, with a blood pressure of 70/30 mm Hg and had marked acrocyanosis (fig 1). The differential diagnosis included a lupus crisis or septic shock. She was treated in the intensive care unit with intravenous ceftriaxone, metronidazole, and prostacyclin for digital ischaemia after serial cultures were taken from all major sites. Staphylococcal toxic shock was excluded, with no growth on vaginal swabs and a negative staphylococcal toxin test. After negative cultures 1 g methylprednisolone was given for a possible flare up of her connective tissue disease. The azathioprine was discontinued. She improved despite concomitant intravascular coagulation. Multiple cultures from all sites did not identify any source of sepsis.

We suspected azathioprine hypersensitivity owing to:

- The timing of the patient’s illness in relation to the initiation of azathioprine
- The presence of recognised features of hypersensitivity—fever, chills, diarrhoea, hypotension, and hepatic dysfunction
- The effect of rechallenge. Three weeks after the presenting episode, one dose of azathioprine 25 mg was given for steroid-sparing effect (the initial illness was attributed to disease flare up); the patient had a more severe and rapid hypersensitivity response requiring treatment with intravenous immunoglobulin and haemofiltration in intensive care.

She improved after treatment with high dose corticosteroids. No cultures ever isolated an infective source.

This case shows the importance of recognising azathioprine hypersensitivity. Approximately 50 cases have been reported in patients with immune mediated diseases such as inflammatory bowel disease, multiple sclerosis, and immune thrombocytopenias, where the initial illness is often ascribed to sepsis or reactivation of underlying disease. Most reactions occur in the first four weeks of drug initiation.\textsuperscript{3} Hypersensitivity should always be included in the differential of fever, hypotension, and renal failure. The case was reported to the Committee on Safety of Medicines (United Kingdom).

The mechanism of the reaction is unclear. Azathioprine is composed of a nitroimidazole attached to 6-mercaptopurine. It is proposed that the imidazole component causes hypersensitivity, while the 6-mercaptopurine may cause haematological side effects. However, there are conflicting reports about the component of the drug to which the hypersensitivity reaction can be attributed.\textsuperscript{4} Fields reviewed 49 cases, where the reaction occurred equally in men and women, aged 16–76 years, and there was a wide variation in azathioprine doses.\textsuperscript{5} All patients who developed shock were also taking corticosteroids. Support for an allergic reaction is that it occurs in only a small percentage of patients,\textsuperscript{6,7} and the event recurs with drug rechallenge, as occurred inadvertently in our patient. Rechallenge with azathioprine is therefore dangerous and should be done under careful observation. A hapten from the imidazole component may bind to a protein molecule to elicit type 1 hypersensitivity. Reactions mimicking sepsis may result from increased production of mediators such as tumour necrosis factor.\textsuperscript{7–9}

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Figure 1 (A) A view of the patient’s feet three weeks after the initial presentation, showing demarcating digital ischaemia; (B) a close up view showing marked digital peripheral ischaemia.
Immunosuppressive treatment for vasculitis associated with Lyme borreliosis

Vasculitis of the central nervous system is a rare complication of Lyme borreliosis. We now report a case of early onset borrelia associated encephalitis followed by systemic vasculitis. Antibiotics failed to improve the clinical course and remission was only reached after extensive immunosuppressive treatment.

A 52 year old man was admitted because of fever, headache, tinnitus, and painful joints. He reported a tick bite on his left arm, which had occurred three weeks earlier and which was followed by a reddish skin eruption. His general practitioner started treatment with doxycycline, but the patient's condition worsened. The patient had a fever of 39.9°C, further physical examination showed no other abnormalities. Except for an erythrocyte sedimentation rate of 51 mm/h and a leucocyte count of 16.1×10^9/l, routine blood analysis was normal. Cultures (blood, urine, stool) were negative. Enzyme linked immunosorbent assays (ELISAs) showed an increased anti-borrelia-IgM titre of 322.5 EU/ml (normal <30) with normal IgG levels, suggestive of early stage Lyme borreliosis. This was supported by western immunoblotting, with numerous splinter haemorrhages distributed over the whole body. Ceftriaxone was continued for 10 days and then replaced by doxycycline. After 18 days antibiotic treatment was discontinued because of lack of improvement. Fever persisted and generalised epileptic seizures complicated the course. Cultures remained negative. An ELISA was repeated after four weeks: the anti-borrelia-IgM was then raised to 800 EU/ml; the IgG level was also above normal. The number of splinter haemorrhages increased and a non-oliguric renal insufficiency developed, resembling a glomerulonephritis with microscopic haematuria, granular casts, and proteinuria (0.9 g/24 h). Screening markers of autoimmune diseases (antineutrophil cytoplasmic antibodies, antinuclear antibodies, cryoglobulins) were negative. A skin-fascia-muscle biopsy sample taken from the right leg showed vasculitis of medium sized arteries (fig 1). No spirochaetes were detected in this sample. Treatment with prednisolone (1 mg/kg/day) did not improve the condition of the patient within one week, therefore, cyclophosphamide (2 mg/kg/day) was added. Within two days the patient regained normal neurological functions. Renal function improved within four weeks (serum creatinine decreasing from 249 to 130 μmol/l, blood urea nitrogen decreasing from 56.4 to 24.4 mmol/l of urea) and the patient was weaned from the ventilator. Follow up was uneventful.

Vasculitis may develop within weeks after infection and complicate the clinical course of Lyme borreliosis. To our knowledge, this is the first description of a systemic vasculitis including cerebral and renal disease after B burgdorferi infection in a human being. Histological proof for vasculitis was assessed in a skin-fascia-muscle sample; the absence of spirochaetes therein suggests an autoimmune based pathogenesis. As in this case, laboratory support for acute B burgdorferi infection is an important issue, especially in areas like the Netherlands. Whether elicited directly by the micro-organism or by secondary autoimmune mechanisms, vasculitis occurs in association with disseminated organ failure. Cyclophosphamide, successful in a case of B burgdorferi induced cerebral vasculitis,16 was effective for this case of systemic vasculitis as well.

In conclusion, persisting vasculitic activity should be suspected whenever antibiotic treatment does not improve the clinical course in Lyme borreliosis. When borrelia associated vasculitis has been histologically established, and does not respond to corticosteroid treatment alone, we suggest the combined use of prednisolone and cyclophosphamide.

Figure 1 Skin-fascia-muscle biopsy sample showing vasculitis of a medium sized artery and some necrosis of the vessel wall.
A 36 year old woman presented with a one month history of pain in the left knee following a week later by pain in the right. The right knee deteriorated over one to two weeks until she was unable to weight bear. There was no pain at rest. At the time of presentation she was 30 weeks pregnant with her first child conceived through in vitro fertilisation. There was no past history of joint problems, alcohol excess, corticosteroid use, or any constitutional symptoms. She walked with two crutches. Joint examination showed a slightly warm right knee with no clinical evidence of an effusion. Both knees were non-tender to palpation but painful at maximal flexion.

Investigations showed an erythrocyte sedimentation rate of 33 mm/1st h, C reactive protein slightly raised at 10 mg/l (normal <3), and globulins at 36 g/l (25–35) with a normal mentation rate of 33 mm/1st h, C reactive protein.

Figure 1 Magnetic resonance imaging at presentation. The T1 weighted sagittal image of the right knee shows diffuse low signal in the posterior aspect of the lateral femoral condyle. Note the low signal fluid in the knee joint cavity.

A diagnosis of transient osteoporosis of pregnancy was entertained and the patient was treated with simple analgesics and followed up closely throughout the remainder of her pregnancy. She presented to the delivery suite in labour at 39 weeks’ gestation and successfully delivered a healthy 4500 g male infant by fast normal vaginal delivery. By three weeks post partum the pain had begun to resolve and she could walk without any aids. At three months post partum there was only residual discomfort in the right knee walking up and down stairs. Repeat MRI of the knees showed dramatic improvement in the bone marrow oedema. In the right knee there was only minor patchy oedema in the distal femur and proximal tibia. In the left knee there was some residual spotty marrow inhomogeneity in the lateral tibial plateau.

Transient osteoporosis is an uncommon condition affecting middle aged men or women in the third trimester of pregnancy. The hip joints are most commonly affected, but the knee is involved in 76% of cases.1 Transient osteoporosis of the hip is a rare condition, with changes only becoming apparent after four to six weeks.2 Demineralisation of the bone and resultant osteopenia may be severe. Joint space is preserved throughout the course and there is no progression to joint erosion.3 MRI is the radiological investigation of choice showing transient bone marrow oedema (the term preferred to “transient osteoporosis”) and almost always a joint effusion.4,5 The cause is unknown, but the MRI appearances and limited histological information6 suggest an active inflammatory process. Although a variety of treatments have been used,7 a conservative approach is favoured during pregnancy.

Anticholesterol antibody levels in patients with systemic lupus erythematosus

Systemic lupus erythematosus (SLE)—the prototype of immune complex diseases—is characterised by disturbances of the cellular and humoral immune systems. Antibodies against nuclear components are the hallmark of SLE, but a number of antibodies against proteins, glycoproteins, and carbohydrates have also been reported. Dyslipoproteinaemias and accelerated atherosclerosis, that commonly lead to coronary artery disease and other complications are recognised sequelae.8-10 The role of autoimmunity in the aetiology of atherosclerosis has recently been highlighted.11 Increased levels of antibodies against oxidised low density lipoprotein, lysophosphatidylcholine, and apolipoprotein A1 were found in patients with SLE.12 As reported earlier, we have shown marked alterations of anticholesterol antibody
(ACHA) levels in patients with various atherosclerotic vascular disorders. In this study ACHA levels of patients with SLE were compared with those of healthy donors.

Sixty eight patients (64 women, four men), aged 39.4 (10.6) (mean (SD)) years, who fulfilled at least four of the diagnostic criteria established by the American Rheumatism Association for SLE1 and 60 healthy donors (55 women, five men), aged 42.6 (8.12), were enrolled into the study. The SLEDAI (SLE Disease Activity Index) score was used to measure disease activity.3 Patients were considered to have active lupus if they scored at least 2 on the modified SLEDAI scale (calculated by omitting anti-dsDNA and complement C3 and C4) and prompt control was obviously indicated to control their symptoms.

The level of cholesterol-specific antibodies was measured by a solid phase enzyme immunoassay described earlier.4 Polystyrene plates (Greiner, Frickenhausen, Germany) were coated with 5 µg/well cholesterol dissolved in 100 µl absolute ethanol and incubated at 4°C for 24 hours. After washing with phosphate buffered saline (PBS) and blocking with 0.1% casein (Reanal, Budapest, Hungary) in PBS, the wells were incubated with 100 µl samples of serum diluted 1:800 in PBS containing 0.1% casein. The binding of ACHA was detected with anti-human horseradish peroxidase conjugated γ-chain-specific rabbit antibodies (DAKO, Glostrup, Denmark) and with o-phenylenediamine (Sigma, St Louis, USA) using H2O2 as substrate. Optical density was measured at 492 nm (reference at 620 nm), and the mean of duplicates was calculated. Serial dilutions of purified immunoglobulin were used as standards in all experiments. Data obtained as optical density values were expressed in arbitrary units per millilitre (AU/ml), related to the standard curve. Our previous observations, in accordance with those of others, demonstrated the specificity of ACHA to cholesterol. The inter- and intra-assay variations of this method were 18.7% and 9.5%, respectively.

Differences between the parameters measured in controls and patients with SLE, between patients with active and inactive SLE, and those between patients with and without previous vascular events were calculated with the Mann-Whitney-test. The χ2 test was used to estimate the discriminative power of ACHA between patients with SLE and healthy donors. The correlation of individual parameters with each other and with the SLEDAI score was calculated using Spearman’s rank correlation test.

Twelve samples (18%) were classified as inactive disease. A number of conditions such as dyslipoproteinaemia,5 nephrotic syndrome, and changes in cholesterol membrane domains6,7 might have elicited the increase of ACHA levels. Corticosteroid therapy might also have stimulated ACHA production, though according to our observations this intervention does not alter ACHA levels significantly. A preventive role against atherosclerosis in patients with SLE has been attributed to raised ACHA levels, though these may also exert an atherogenic effect.8 Further studies are necessary to clarify the role of ACHA in the changes of lipid metabolism ascertained in patients with SLE.

This work was supported by grants OTKA No T 029044 (IK) and ETT No 239/2000 (LR).

Sjögren’s syndrome: an unusual cause of Bell’s palsy

The most common form of facial paralysis is idiopathic—that is, Bell’s palsy. Sjögren’s syndrome (SS), a chronic inflammatory disorder characterised by lymphocytic infiltration of exocrine glands resulting in the so called “sicca complex”, is a rare secondary cause of this self limiting illness. Primary SS includes mostly peripheral, and to a lesser extent central, autonomic neuropathy and central nervous system involvement.1 A patient with unilateral facial palsy, autoimmune hypothyroidism, and Sjögren syndrome is presented.

A 41 year old woman developed right sided facial numbness, described as “dentist anaesthesia for tooth extraction”. One day later she had a reduced sense of taste and right facial weakness. General physical examination was not remarkable. Neurological examination showed anisocoria, peripheral right sided facial paresis, reduced sense of taste on the right half of the tongue, and dysaesthesia in the region of the second segment of the right trigeminal nerve.

Although the erythrocyte sedimentation rate (ESR) was 30 mm/1st h, routine laboratory investigations were normal, including, IgG, IgM, IgA levels, and autoantibodies. Magnetic resonance imaging (MRI) of the brain showed no abnormalities. Nerve conduction studies showed peripheral facial paresis. She recovered spontaneously from her symptoms within seven days, and ESR, during follow up the raised ESR persisted.

Review of her medical history uncovered complaints of burning eyes and dry mouth, slight weight gain, and cold intolerance. There was a history of arthralgias or skin lesions.

There was no history of arthralgias or skin lesions. She recovered spontaneously from her symptoms within seven days, and ESR, during follow up the raised ESR persisted.

focus score of one lymphocyte focus for 4 mm²
salivary gland tissue. Additionally, thyroid
function tests showed a raised thyroid stimu-
lating hormone (11 mU/L), low free thyroxine 4
(13.0 pmol/L) with positive antithyroid micro-
somal antibodies and negative antithyroglobu-
lin antibodies.

The clinical, serological, and histopatho-
logical manifestations fulfilled the European
study group criteria for the diagnosis of SS.
The patient was treated with artificial tears and
thyroxine supplements that returned her
thyroid function tests to normal.

Prevalence of neuropathy in patients with SS
ranges from 10 to 50%. Polynuropathy
is the first clinical manifestation of SS
and may even precede sicca symptoms in
40% of patients. However, less frequently,
cranial neuropathy can occur with a predis-
position to involvement of the trigeminal
nerve. The vasculitic damage to vaso nervo-
rum documented by pathological studies is
associated with a higher incidence of serum
ANCA* (anti-PR3* or anti-MPO*).

The association of SS with autoimmune thyroid disease
(AITD) is well recognised. To our knowledge the com-

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matic recognition of the trigeminal
nary to AITD has not been reported hitherto.

The association

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Antitrypsin phenotypic variability is not
associated with ANCA in southern Chinese

Antitrypsin (α1T) is a 52 kDa protein
encoded by a gene locus P1 on chromosomal
segment 14q32.1. It is a natural inhibitor of
proteinase 3 (PR3), a neutrophil granular
protein and a major autoantigen of antineu-
tral antibodies.

The function of α1T is in turn restricted by
myeloperoxidase (MPO), another autoanti-
gen of ANCA. The interplay between the
enzymes, inhibitors, and the autoantibodies
is implicated in the dynamics of the vasculitic
process, resulting in a whole spectrum of
clinical conditions ranging from systemic
granulomatous diseases to kidney limited
glomerulonephritis. There have been reports of
the correlation of specific α1T alleles, notably Z, with ANCA. 

These were 1AT alleles, but this did not reach significance
in Chinese patients with a clinical diagnosis of
primary Sjogren’s disease. Acta Neurol Scand

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Table 1 α1T phenotypes in ANCA* (anti-PR3* or anti-MPO*) positive patients

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*ANCA = antineutrophil cytoplasmic antibody; PR3 = proteinase 3; MPO = myeloperoxidase.

Table 2 α1T phenotypes in ANCA* (anti-PR3* or anti-MPO*) positive patients

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<td>0(0)</td>
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<td>Other</td>
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<td>1(1)</td>
<td>1(0.5)</td>
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Total 314(100) 120(100) 194(100)

*ANCA = antineutrophil cytoplasmic antibody; PR3 = proteinase 3; MPO = myeloperoxidase.
associated diseases in southern Chinese among whom anti-MPO predominated.

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A case of cholesterol embolism with ANCA treated with corticosteroid and cyclophosphamide

We report a case of a patient with cholesterol embolism who showed positive for both myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) and proteinase 3 antineutrophil cytoplasmic antibody (PR3-ANCA) and who was treated with prednisolone (PSL) and cyclophosphamide.

A 50 year old man underwent cardiac catheterisation for back pain. The examination disclosed 90% stenosis of the right coronary artery and a saccular aneurysm in the thoracic aorta. The patient underwent percutaneous transluminal coronary angioplasty and the aneurysm was wrapped with an artificial blood vessel. Postoperatively, the patient had a fever, pleural effusion, abdominal pain, and increased white blood cell (WBC) count, C reactive protein (CRP), and serum creatinine. The absence of blood and pleural exudate were negative. PSL 15 mg/day was started. However, acute progression of renal failure required haemodialysis. The patient was transferred to our hospital.

Physical examination showed a temperature of 38.0°C and blood pressure of 178/98 mmHg. Cyanosis was noted in both heels and all toes with necrosis and ulcers at the tips of the fifth toes. He had an increased erythrocyte sedimentation rate (ESR) of 82 mm/1st h. Anaemia was noted with a red blood cell count of 2500×10³/l, while the patient’s WBC count was high at 12×10⁹/l. His platelet count (304×10³/l) was within the normal range. Biochemistry showed high levels of blood urea nitrogen (10.0 mmol/l of urea), creatinine (710 mmol/l), and CRP (11.3 mg/l). Complements components were within normal ranges. PR3-ANCA and MPO-ANCA were high at 82E and 29E, respectively.

After admission to hospital, circulatory disturbance in his toes worsened. A diagnosis of ANCA associated vasculitis was made based on systemic inflammatory findings and high levels of WBC, CRP, PR3-ANCA, and MPO-ANCA. High dose steroid treatment was started. Biopsies of the right heel skin and thigh quadriceps showed cholesterol embolism (fig 1). However, PSL treatment was continued together with three courses of cyclophosphamide pulse treatment because of persistent fever and high ANCA values. The treatment reduced the fever and toe necrosis, and the ulcers improved. ANCA gradually decreased to normal. The PSL dosage was reduced to 15 mg/day and the patient was discharged.

Cholesterol embolism predominantly affects elderly men with a history of hypertension, atherosclerotic vascular diseases, and renal insufficiency at the time of diagnosis. At least 31% of patients had a preceding history of anticoagulant use or the antecedent performance of a vascular procedure affecting the arterial circulation. The presence of these cholesterol embolisms within the vascular lumen triggers a characteristic localised inflammatory and endothelial vascular reaction. The inflammatory changes resulting from cholesterol embolism may be responsible for many of the systemic manifestations such as fever, weight loss, myalgia, leukocytosis, eosinophilia, and a raised ESR. Thus cholesterol embolism is referred to as both vasculitis look-alikes and pseudovasculitis syndrome. The prognosis is poor, particularly in the presence of acute renal failure. Three ANCA positive cases of cholesterol embolism have been described. Peat and Matheson reported an ANCA positive patient with dyspnoea and haemoptysis after acute deterioration of renal function. Cyclophosphamide and PSL improved the symptoms, but cyclophosphamide was discontinued and the PSL dose was reduced because renal and skin biopsies showed cholesterol embolisms. Subsequently, the patient died of intractable cardiac failure.

Kaplan-Pavlovic et al reported two cases of renal failure with positive MPO-ANCA. The details are unknown for one patient. The other patient was treated with corticosteroid alone. This patient required haemodialysis and amputation of the toes. Although their treatment did not result in the improvement of vasculitis, the combination of PSL and cyclophosphamide was effective in our patient with ANCA.

This result suggests that active treatment with corticosteroid and cyclophosphamide should be considered in ANCA positive cases of cholesterol embolism.

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No renal biopsy was performed in these patients. 

Several antirheumatic agents have been reported to induce renal manifestations or drug induced lupus reactions, or both, in patients with RA. In these subjects a genetic predisposition for HLA has been previously suggested. 

To determine whether similar genetic factors might be operative in auranofin induced nephropathy, we analysed the HLA-DRB1, DQA1, and DQB1 alleles using a polymerase chain reaction. Furthermore, we investigated if the renal side effects were associated with serological findings in accordance with systemic lupus erythematosus (SLE), thus indicating the development of a drug induced lupus reaction. 

Six patients (three female, three male) who developed biopsy proven membranous nephropathy or significant proteinuria (>0.5 g/day) during treatment with auranofin are reported. All patients met the American College of Rheumatology criteria for RA. The median age before onset of auranofin treatment was 72 (52–83) years, 4/6 patients were rheumatoid factor positive and 2/5 patients were antinuclear antibody (ANA) positive. The median duration of auranofin treatment before the onset of proteinuria was 5 (4–10) months. During auranofin treatment, two patients developed an increased ANA titre (1:200 and 1:1600) but no antibodies against anti-dsDNA, SSA/SSB, Sm, or RNP were detected. None of the patients developed an increased serum creatinine level. After withdrawal of auranofin, proteinuria decreased significantly or disappeared in all cases. 

Table 1 presents the HLA alleles. A high frequency of the alleles associated with SLE—namely, DRB1*0301 (DR3), DQA1*0501, and DQB1*0201, was recorded in the patients developing membranous nephropathy or proteinuria during auranofin treatment. Of these, DRB1*0301 and DQA1*0501 occurred in 4/6 of the patients, and 5/6 patients carried at least one of these alleles. The importance of DR3 or DQA1*0501 in drug induced renal manifestations has previously been suggested in patients with penicillamine and sodium aurothiomolate induced renal side effects. Also, in accordance with these findings, the DQA1*0501 and DRB1*0301 alleles have been recorded in a high frequency in patients developing sulfasalazine induced nephritis. 

In two cases the development of membranous nephropathy was accompanied by a simultaneous increase in the ANA titre, thus indicating development of a drug induced SLE reaction. However, both patients had previously presented some sign of an autoimmune reactivity pattern, which may confer a risk factor in the treatment with certain antirheumatic drugs in RA. 

Simultaneous treatment with sulfasalazine had been given in two cases, but as the sulfasalazine treatment period was either limited, or lacked any time relation with the onset of proteinuria, it seems unlikely that the patients developed a drug reaction against sulfasalazine. Further arguments rejecting the possibility of a sulfasalazine induced drug reaction are the lack of anti-dsDNA antibodies and the rapid onset of proteinuria among the patients, thus contrasting with the findings reported in sulfasalazine induced SLE. 

The mechanism for induction of membranous nephropathy during auranofin treatment is unknown. Interestingly, it has been suggested that gold can bind to and alter major histocompatibility complex-peptide complexes, thus giving a possible explanation of both beneficial effects as well as side effects during treatment. Another possibility is that auranofin may alter the cytokine pattern towards an SLE-like phenotype and thus facilitate the development of SLE associated manifestations in genetically susceptible subjects. In accordance with this hypothesis, auranofin or other gold preparations have been reported to inhibit the production of interleukin 1 (IL1), tumour necrosis factor α, and IL2. The effects on IL10, a cytokine reported to be increased in both patients with idiopathic SLE and their healthy relatives as well as in patients developing sulfasalazine induced SLE-like reactions, is unknown, however. 

In conclusion, the data suggest that SLE related HLA alleles, with special focus on DRB1*0301 and DQA1*0501, may predispose to development of renal side effects or drug induced lupus reactions during treatment with auranofin, as also previously recorded during treatment with other antirheumatic agents. Development of drug induced SLE, here reported for the first time, may occur during auranofin treatment.

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