LETTERS

Cladribine in the treatment of systemic lupus erythematosus nephritis

Systemic lupus erythematosus (SLE) nephritis often requires treatment with cyclophosphamide, which carries the risk of major side effects including infection, ovarian failure and bladder malignancy. Therapeutic strategies that would specifically target lymphocytes are appealing. Following the first report of the use of the purine nucleoside analogue cladribine (2-chloro-2'-deoxyadenosine), a selective lymphocyte depleting agent, in the treatment of lupus nephritis,1 we report our experience in two patients with severe renal involvement.

CASE 1
A 32 year old woman was diagnosed with SLE at age 28, with polyarthritids, photosensitive rash, subcutaneous nodules, fatigue and lymphopenia. ANA, anti-dsDNA, anti- Sm and anti-RNP antibodies were present. Various immunosuppressants and corticosteroids failed to maintain a sustained remission. Two and a half years after presentation, she developed haematuria and proteinuria and renal biopsy revealed WHO Class III lupus nephritis. Treatment with pulsed intravenous cyclophosphamide and methylprednisolone were subsequently added. Pulse intravenous cyclophosphamide in the interim had failed to control her disease. Cyclophosphamide, additionally, had resulted in premature ovarian failure. Repeat renal biopsy showed progression to Class IV nephritis with focal necrosis and crescents. Cladribine (continuous IV infusion of 0.05 mg/kg/day for seven days) and prednisolone 40 mg/day proved ineffective as creatinine rose from 149 to 243 µmol/l in two months. She also developed a perineal herpes simplex infection but drug was otherwise well tolerated. Pulse intravenous cyclophosphamide and methylprednisolone were subsequently reintroduced and creatinine has again fallen to 118 µmol/l.

Table 1 shows the results of investigations before and after cladribine infusions for both cases.

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<td>292 IU/ml</td>
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Leg bone pain syndrome in a kidney transplant patient treated with tacrolimus (FK506)

Patients with chronic renal failure often develop musculoskeletal problems such as renal osteodystrophy and amyloid arthropathy,2 and in successful renal transplantation other complications may ensue, particularly avascular necrosis.3 Since the availability of immunosuppressive agents for rejection, there has been a decrease in musculoskeletal problems, however, new complications have been described such as a symmetrical bone pain syndrome and reflex sympathetic dystrophy syndrome (RSDS), some of them related to cyclosporin.4

Tacrolimus is a novel macrolide with potent immunosuppressive effects and with a very similar mechanism of action to cyclosporin A—that is, calcineurin phosphatase inhibition.5 We report on a patient treated with tacrolimus, who developed a leg bone pain syndrome, two months after kidney transplantation.

The patient was a 50 year old woman with severe hypertension, treated with atenolol (100 mg/day), verapamil (240 mg/day) and clonidine (0.150 mg/day). She developed chronic renal failure and was treated with peritoneal dialysis in 1995. In 1997 she underwent a kidney transplant from a cadaver and immunosuppressive treatment with tacrolimus (4 mg/day) and prednisone (15 mg/day) was started. Two months after transplantation she reported progressive bilateral symmetric pain in the knees. Because of pain and difficulty in walking she was readmitted to our unit. At this time, the patient was receiving tacrolimus (4 mg/day) and prednisone (5 mg/day). Clinical examination revealed pain on movement and tenderness over the bone and joint line, without swelling.

Table 1 Results of investigations before and after cladribine infusions

Reference ranges: serum creatinine 50–100 µmol/l, anti-dsDNA: 50–300 IU/ml positive, >300 IU/ml strongly positive, C3: 0.63–1.19 g/l, C4: 0.11–0.43 g/l, C3d: up to 12 units/ml.
or increased temperature. She had no signs of autonomic vasomotor disturbances and arterial mobility was normal. Examination of the remaining peripheral and axial joints was normal.

Blood tests showed creatinine levels of 1.3 mg/dl, calcium of 10.1 mg/dl, phosphate of 3.5 mg/dl and urate of 7.2 mg/dl. Other laboratory findings were normal. Patchy osteoporosis in the knees was seen radiographically. Bone scintigraphy showed intense uptake in both the osseous and vascular phases in the knees (fig 1). Calcitonin treatment was begun (three monthly cycles of 10 intramuscular units/day during 20 days) without clinical improvement. Because of the high serum concentrations of tacrolimus (15 μg/ml) and the ineffective calcitonin treatment, tacrolimus was reduced to 2 mg/day. Nine months after transplantation, she was free of symptoms and radiographs and tacrolimus concentration (9.1 μg/ml) were normal. Changes in plasma tacrolimus concentrations subsequent to the resolution of symptoms did not occur and the patient continued asymptomatic.

We describe a complication in a patient treated with tacrolimus after kidney transplantation that is similar to that described by other authors in transplanted patients treated with cyclosporin. Although the radiographic and bone scintigraphy findings suggested RSDS, the symptoms of this patient were not the classic features of this entity. The efficacy of corticosteroids in the treatment of uncompli- cated RSDS has been demonstrated, it is possible that corticosteroids might have a protective role against a full RSDS development, as she was treated with high doses of prednisone after the renal transplantation.

The early onset of symptoms after the administration of the drug and the clinical improvement after the reduction of the immunosuppressant dose, are features that support a possible relation between tac- rolimus and the leg bone pain syndrome. The patient had high plasma tacrolimus concentrations at the onset of the clinical symptoms and the improvement appeared only when the drug doses went down. Although recurrence of knee symptoms with an increase in tacrolimus dose would be much stronger proof of this association, it is not ethically justifiable. Furthermore, she was treated with verapamil in addition to other drugs for controlling hypertension. Verapamil might have played a part in a possible increased risk for this clinical complication, because it decreases tacrolimus clearance. However, there are reports that calcium channel block-
formed successfully in some patients.

parenchyma. (white) area consistent with infarction was by computed tomography. Large firm yellow spleen shows changes corresponding to those seen

Figure 2 Cut gross pathological section of a normal sized spleen with only subcapsular neutrophil infiltrate has been described in a patient who subsequently developed full-blown WG. In another case, a spontaneous splenic hemorrhage was ascribed to vasculitis in a patient who had severe WG that required hemodialysis. 

In our two patients, microscopical study of the spleen also showed hemorrhagic infarction caused by specific WG related vasculitis process. A severe splenic haemorrhage occurred in patient 1, which was clearly related to both necroting vasculitis and hypocogulable state. Anticoagulation was indicated for inaugural myocardial infarction in case 1 and deep venous thrombosis in case 2, in both cases during active WG flare. Splenectomy was required in both our cases.

Our data suggest that antithrombotic treatment entails a specific risk of bleeding complications in patients with WG vasculitis. When anticoagulation is necessary in WG patients, computed tomography of the abdo- men should be systematically performed and, if splenic infarction is disclosed, splenectomy should be considered.

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10. Morayati SJ, Fink-Bennett D. Indium-111 leu-

11. Kettirits R, Anders S, Kettirits U, Schneider W, Gobel U. LUFT PC. Spontaneous splenic hemorrhage in a patient with Wegener’s granu-


13. Franssen CFM, Ter Maaten JC, Hoornse SJ. Spontaneous splenic rupture in Wegener’s vas-

Amiodarone induced lupus

Lupus related to amiodarone has not previ-
ously been described. We report on a patient who developed drug induced lupus (DIL) in association with amiodarone treatment. To our knowledge, this is the first report of amiodarone induced lupus (CD ROM: Medline, USA National Library: 1956–98).

A 71 year old white woman was admitted because of two weeks of pleuritic chest pain, dyspnea on exertion, and non-productive cough. She had malaise, intermittent fever, arthralgia, and weight loss for more than six months. There was no history of Raynaud’s phenomenon, oral ulcers or photosensitivity. She had a six year history of arterial hypertension and atrial fibrillation treated with amiodarone, digital and amiodarone (200 mg twice daily) for the past 10 months.

Physical examination disclosed malar rash, an aortic systolic murmur (grade II/VI), and hypoventilation in both pulmonary bases. Laboratory studies showed an erythrocyte sedimentation rate of 90 mm 1st h. Peripheral blood examination revealed a mild normochromic and normocytic anaemia (10 g/dl), normal white blood cells count (4000 µl), with lymphopenia (20 per cent), and normal platelet count (180 000/µl). Coagulation tests were normal. All serum chemistries, including thyroid function tests, creatinine phosphokinase, immunoglobulins, comple-
ment levels, and urine analysis were within normal limits. Coombs’s tests were negative. Rheumatoid factor was 1:320. Circulating immune complexes (IgG-C1q) were positive. Antinuclear antibodies (ANAs) were positive at 1:640; anti-Ro, anti-La, anti-dsDNA, anti-Sm, anti-histone antibodies, antiphospho-
lipid antibodies, cryoglobulins, C reactive protein, VDRL and Mantoux test were nega-
tive. Blood and urine cultures were negative. Electrocardiogram was within normal limits, and the two dimensional echocardiogram showed mild aortic stenosis. Chest radiogra-
phy revealed bilateral pleural effusions, with-
out fibrosis or cardiacomegaly. Pleural fluid was exudative, with lymphocytic predominance, without cytological features for malignancy. Cultures of pleural fluid for bacteria, includ-
ing for Mycobacterium tuberculosis, were nega-
tive. Bone scan with technetium-99m showed increase uptake in hands, elbows, and knees. The histopathological examination of biopsy specimens of the skin, including indirect immunofluorescence stain, muscle and tem-
poral artery did not show abnormal features.

The amiodarone was stopped and the patient progressively improved. No cortico-
steroids were given. On the third week she developed a transient relapse, with fever, malaise and with evidence of unilateral pleu-
ral effusion. One year after no clinical, analytical or radiological findings were present, and three years later she still remained free of symptoms, and the ESR, complete blood count, and radiological data were normal. The titre of ANA decreased but remained weakly positive at 1:40.
patients with DIL are usually older; the prevalence of men and women is similar and the presenting symptoms are usually mild, with the patient usually complaining of malaise, fever and arthralgia, with or without arthritis, while skin, central nervous system or renal involvement is rare. Pleuropneumonial disease is frequent and, as in classic SLE, anaemia and leucopenia may be present. Serum complement components are usually normal, ANAs are positive but anti-dsDNA and anti-Sm are negative, while anti-histones antibodies can be detected in most of patients.1

The pathogenic mechanisms proposed for DIL include: cross reactivity between drug and the nucleic acid; hapten complex formation between drug and nucleic acid, or structural damage to the chromosomal DNA; action of drug as an adjuvant or immunostimulant, which, in concert with appropriate immune response genes, triggers polyclonal B/T cell activation; and interference with the complement pathway.1

The incidence of side effects associated with amiodarone ranges from 40% to 94% and, in most cases, these side effects are consequence of its potential to be directly toxic to several organ systems.2,3 However, there is also some evidence of immunologically mediated phenomena related to amiodarone. A positive skin and basophil degranulation test with amiodarone, secretion of leukocyte inhibitory factor, positive lymphoblastic transformation and circulation of a specific antibody of the IgG class have been described.4 Moreover, several studies suggest that various biological and immunological markers of “systemic” disease activity are present in patients taking this drug. Circulating immune complexes, ANAs, and non-specific increase in ESR and white blood cell count, sometimes with eosinophilia, are common findings.5

ANA titre is not uncommon in an elderly patient. However, spontaneous SLE in elderly people is not usual and DIL must always be considered in the differential diagnosis. This case, presenting with malaise, fever, arthralgia, circulating immune complexes, and autoantibodies strongly suggests an immunological underlying condition. Moreover, this patient meets four SLE criteria: malar rash, serositis, haematological disorder (lymphopenia), and positive ANAs test. Imputability criteria of amiodarone induced lupus are present on a semiological basis with disappearance of most of the symptoms after amiodarone withdrawal. The relapse could be explained because of the long elimination half time of the drug and, in consequence, the immune response might progress despite discontinuation of the treatment.

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Antinuclear antibodies in relapsing polychondritis

The prevalence of antinuclear antibodies (ANA) in relapsing polychondritis (RP) has recently been reported by Zeuner et al6 as high as 66%,1 usually in a low titre with a speckled pattern. We report here on our experience of ANA testing in patients with RP.

The charts of 180 patients followed up in our institution fulfilling the criteria for RP proposed by Michet et al2 have been recently retrospectively reviewed with special focus on dermatological manifestations and their relation with myelodysplasia.3,4 This aim led us to exclude 36 patients because the association of RP with potentially confounding factors—such as systemic lupus erythematosus, Sjögren’s syndrome, or acquired myelodysplasia—agrees with the negative results of these 36 patients, strong ANA positivity was found in eight patients. All five patients with MCTD had ANA > 1/1000 (in a speckled pattern in four), with positive antibodies to RNP and negative tests for dsDNA. The two remaining patients with another connective tissue disorder—agrees with the negative results of tests for IgG antinucleosome antibodies recently reported by our group in this condition.

We conclude that: (a) the prevalence of ANA observed in RP is low and, (b) as suggested by other authors,5 the finding of a significant titre of ANA in a patient with RP strongly suggests the presence of an associated disorder, such as SLE, MCTD, Sjögren’s syndrome or acquired myelodysplasia.
There is no association between polymyalgia rheumatica and acute parvovirus B19 infection

Parvovirus B19 has been associated with a growing number of diseases. Besides the frequent manifestations such as erythema infectiosum or hand-foot-mouth disease in persons with underlying haemolytic anaemia, hydrops fetalis in pregnant women and acute or chronic arthritis a range of rather rare diseases have been described in recent reports. Among them are case reports on persistent parvovirus B19 infection in immune incompetent people, encephalitis, myocarditis, systemic lupus erythematosus (reviewed by Anderson and Young) and juvenile chronic arthritis. Furthermore, parvovirus B19 has been suspected to play a part in the aetiology of polymyalgia rheumatica (PMR).

Because of the acute onset of PMR and its systemic symptoms an infectious agent may be a relevant factor. Additionally, autoimmune processes have been demonstrated in both, PMR and parvovirus B19 infection. As the receptor for parvovirus B19, the F-blood group antigen (glucosamine), is also present on endothelial cells an interrelation between parvovirus B19 and giant cell arteritis or PMR may be possible. Parvovirus B19 can only replicate in erythroid precursor cells in human bone marrow, but it is known that infection of cells non-permissive for viral replication leads to an excess production of the viral non-structural protein (NS1) without production of capsid protein. It may be the NS1 protein which is cytotoxic and able to induce apoptosis, it probably plays a part in the pathogenic process of the parvovirus B19 induced tissue damage. This is confirmed by the fact that antibodies against the non-structural protein NS1 of parvovirus B19 are preferentially produced during chronic or persistent parvovirus B19 infections, for example in parvovirus B19 associated chronic arthritis.

To test the hypothesis whether PMR is associated with acute parvovirus B19 infection, we tested the seroprevalence of IgG antibodies against the two structural proteins VP1 and VP2 and against the non-structural protein NS1 in 110 PMR patients (patients with giant cell arteritis excluded; mean (SEM) age 67.0 (0.8) years, range: 48–77) and, for comparison, in 135 healthy controls of different ages. At the time point of blood sampling (median disease duration at the time point of blood sampling: 0.6 years, range: 0–7.3, mean (SEM): 1.4 (0.2) years), 35 patients had no corticosteroids and 75 patients received on an average 15.2 (1.8) mg prednisolone/day. Furthermore, we investigated the presence of NS1 specific antibodies in healthy controls and patients with PMR. Non-parametric Kruskal-Wallis one way analysis was used to compare means of different subgroups. The significance level was p<0.05.

Subjects in the control group had various ages between 18 to 75 years. Overall seroprevalence of IgG against the capsid proteins VP1 and VP2 was 78% (fig 1). Overall IgG seroprevalence against VP1 and VP2 was 88% in patients with PMR (not significantly different versus the age matched control group). With respect to the NS1 IgG antibody, overall seroprevalence in the control group was 22% (fig 1) and in patients with PMR 20% (p=0.057 versus the age matched control group).

Furthermore, we investigated the association between the presence of NS1 IgG antibodies and PMR related symptoms or laboratory parameters (patients with NS1 IgG antibodies were not different in age, sex, and medication). The symptoms were assessed using standard record forms from the medical history (at the time serum was collected). We asked the patients for muscular pain in the left/right shoulder, left/right upper arms, left/right neck, left/right gluteal muscle, and left/right thigh. If one muscle group was painful the corresponding item was scored with one point (the sum of the item points was the overall muscle score). In PMR patients with NS1 IgG as compared with patients without NS1 IgG, arthralgia was more frequent (versus without: 73% vs 40%, p=0.024). However, the overall muscle score was lower in NS1 positive than in NS1 negative patients (0.5 (0.2) SEM v 1.6 (0.3) SEM score points; p=0.021). With respect to other PMR related symptoms, no significant differences were found. In patients with a positive NS1 IgG antibody, interleukin 6 (4.6 (0.9) SEM v 11.3 (2.2) SEM; p=0.037) and soluble ELAM (48.2 (4.8) SEM v 71.4 (5.2) SEM; p=0.024) were significantly lower as compared with patients without NS1 IgG. Furthermore, disease related immune mediators such as interleukin 6 or soluble ELAM were lower in patients with as compared with patients without NS1 IgG. As a positive NS1 IgG indicates an active infection, an acute parvovirus B19 infection does not seem to be a pathogenetic factor in our patients with PMR.

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Neutrophil chemotaxis in Behçet’s syndrome

It has been suggested that the marked cellular inflammatory response, which characterises Behçet’s syndrome (BS), may be attributable to increased neutrophil locomotion. However, others disagree. We have re-evaluated chemotaxis of polymorphonuclear leukocytes (PMNs) in BS among a greater number of patients in a controlled setting.

Fifty four male BS patients, nine male patients with ankylosing spondylitis, eight with psoriasis and 37 male healthy controls were studied with 28 female patients with BS and 16 healthy female controls. Behçet patients with severe disease were those with active oral ulcers and eye involvement.

We measured chemotaxis with the “under the agarose method”. The measurements were masked with the assessors not knowing the diagnoses. An inverted microscope fitted with an ocular micrometre disc to measure the migration of neutrophils from middle wells to outer (chemotaxis) and inner wells (chemokinesis) was used. Zymosan activated sera (patients or controls) were used as a source of C5a. Results were expressed as micrometre square (1 mm²=8 squares). Additionally the plates were evaluated macroscopically for the observation of the migration between neutrophil wells.

Tables 1 and 2 show the results. There were no significant differences between the chemotactic indices of the various groups of patients and controls studied of either sex. Maximal chemotaxis rates in the groups varied from 67% to 100%.

The Boyden millipore filter system has extensively been used for chemotaxis experiments. The agarose method is simple and cheap. This method can preferentially differentiate chemokinesis from chemotactic migration.

There is marked heterogeneity in disease expression in men and women in BS and we reasoned that some of the confusion in the literature about neutrophil activity might be related to this. Thus we analysed our data separately for either sex.

It has been suggested that the marked cellular inflammatory response, which characterises Behçet’s syndrome, is responsible for increased neutrophilchemotaxis. In the Carletto study clinically active Behçet patients demonstrated increased chemotaxis to sera by Senn’s modified in vivo assay. Others had found hyperchemotaxis to be more responsible fractions again by using an in vivo assay. Although it is difficult to compare the results of in vitro and in vivo assays, we thought these reported increases might have resulted from increased chemokinesis. In our experiments we observed maximal chemotaxis (3 mm) frequently, however, we did not find any significant differences in chemotactic indices between diseased and healthy subjects.

An interesting aspect of our study was the migration between neutrophil wells that was observed in many of the Petri dishes. This was observed even though we had not used cellular materials as chemotactic agents. Presumably the gravity of the cellular materials overcame the chemical gradient of zymosan activated sera in some Petri dishes. Because of the observed migration between neutrophil wells, we suggest that there should be only one “triple well rank” in a Petri dish. On the other hand our method of preincubation of the whole blood for 45 minutes at 37°C before harvesting the PMNs (intended for better viability) might have been responsible for this phenomenon by increasing the chemotactic activity in all groups studied. Further studies are needed to clarify these issues.

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<td>Healthy controls</td>
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<td>*Kruskal-Wallis one way analysis of variance, corrected for ties: χ²=2.1381, DF=4, p=0.58.</td>
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<th>Table 2 Chemotactic indices in women*</th>
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<td>*t=0.32, p=0.05.</td>
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Neuropsychiatric systemic lupus erythematosus

The considerable difficulties in making sense of the literature on patients with lupus involving the central nervous system are re-emphasised in the paper by Rood et al. The authors, who do refer to a reasonably cautious approach to their results, nevertheless seek to persuade us that the IL10 locus is associated with neuropsychiatric lupus on the basis of a historical case notes review of 42 lupus patients with neuropsychiatric disease, compared with 50 who lack such involvement.

The authors disagree that CNS lupus is attributable to either antiphospholipid antibody related thrombotic events, or “immune mediated” disease. This discussion is artificial. There is a considerable literature on CNS lupus that proposes that a wide variety of immunopathogenic mechanisms may be responsible in individual cases. These mechanisms include thrombotic effects, which may be linked to antiphospholipid antibodies, a true vasculitis, a cross reaction between antibodies that recognise the lymphocyte surface targets and neurologic antigens, and antibodies to a wide variety of neurological targets. A considerably larger number of patients will have to be studied before any claims of links to an IL10 promoter haplotype can be truly convincing.

We agree with the authors that patients with SLE have a higher innate production of IL10 than controls. However, as there is no significant difference in the frequency of the IL10 promoter single nucleotide polymorphism (SNP) in SLE patients when
compared with controls in their study, we suspect that the difference in IL10 production is not attributable to functional differences between patients with SLE and controls in terms of the IL10 SNP alleles frequencies. Differences have been described with respect to microsatellites and one awaits confirmation from other populations or family studies. To our knowledge, a difference in IL10 production between patients with neuropsychiatric disease SLE and non-neuropsychiatric disease SLE has not been described. The described associations would be biologically meaningless if IL10 production is similar between these two groups.

The authors suggest that the -1082A allele is associated with a higher innate IL10 production, however, they appear to ignore the only published study to date that showed that the A allele was associated with lower IL10 production.4 In addition, we have confirmed that the A allele is associated with lower IL10 production in transient transfection studies and the ATA/ATA genotype is associated with IL10 production in whole blood culture.5 The increase in the A allele is mainly accounted for by an increase in the ATA haplotype in their neuropsychiatric disease patients and therefore they are described with a low IL10 producing haplotype, not a high IL10 producing haplotype. One interpretation of this would be that patients with neuropsychiatric disease symptoms are unable to adequately control inflammation from a variety of different pathological mechanisms because of low IL10 production.

**Authors’ reply**

We thank Drs Isenberg, Crawley and Woo for their interest in our paper. They argued that the dichotomy of the pathogenesis of CNS lupus in “immune mediated” and thromboembolic disease is too rigid, but believe that pathogenetic mechanisms can be deemed responsible for CNS lupus. As the hallmark of SLE is the production of autoantibodies, it seems to be justified to assume that the pathogenetic role of CNS lupus is B cell mediated. Based upon this assumption we clustered the individual neuropsychiatric disease SLE patients and tested the hypothesis that a genetic marker in the promoter of the IL10 gene is associated with the phenotype of CNS-SLE.

In general, a positive result in a genetic association study is only possible after a correct definition of the phenotype. After all, if the phenotype is not well defined, the magnitude and statistical significance of the association will be less or lost because of the random distribution of the genetic marker in the unclassified patients. If misclassification occurred in the sense that CNS lupus patients were attributed to the non-neuropsychiatric disease SLE population, the fact that we still found a positive result strengthens our conclusions instead of weakening it.

It might be argued that thromboembolic events do not fit in the pathogenetic model of B cell mediated CNS lupus. But, as stated clearly in the article, even after exclusion of these ambiguous patients the distribution of the frequencies in the neuropsychiatric disease SLE and non-neuropsychiatric disease SLE patients remains the same.

Of course we agree with the notion that our findings must be repeated in an independent group of patients. Interestingly, the increased prevalence of ATA in neuropsychiatric disease SLE patients has already been reported by Mok in a group of Chinese SLE patients.4 Currently we are investigating the distribution of the IL10 promoter haplotypes of neuropsychiatric disease SLE patients in an ethnically different population.

In our article we have elaborated on two possible explanations of our findings. Firstly, the increased frequency of the ATA haplotype might be associated with an increased production of IL10. We made this assumption in the light of previous studies stating that SLE as a whole is characterized by an increased IL10 production.4,5 It is wrong to extrapolate these conclusions to our population. Because of the retrospective character of our study, we were not able to measure IL10 production in each of our patients. Therefore, we cannot say whether or not IL10 production in our SLE patients as a whole was similar to or different from the control population. It might well be that differences in IL10 production would only emerge after stratifying into neuropsychiatric disease SLE and non-neuropsychiatric disease SLE patients. Furthermore, it might be that in the populations mentioned above, there was an excess of patients with neuropsychiatric disease SLE.

The second explanation for the skewing found in IL10 promoter polymorphisms might be that the genetic susceptibility to neuropsychiatric disease SLE in the ATA patients is not conferred via an increased IL10 production at all, but that it is merely a marker for the real neuropsychiatric disease SLE susceptibility allele. It is not clear whether or not IL10 promoter SNPs are associated with low or high IL10 production, because of the ambiguous reports in the literature. In our laboratory, the -1082A allele has been found to be associated with high IL10 production. In this light we have speculated about the possible link of high IL10 production and the pathogenesis of neuropsychiatric disease SLE. Inseberg et al have referred to another group stating that -1082A is associated with a low risk IL10 production and they interpret our results with this finding in mind.4 In conclusion, we do not know the relevance of the IL10 promoter in the in vivo regulation of IL10 production and therefore both explanations are equally speculative.
translation may occur. This compares with the iron regulated pathway of ferritin synthesis in haemachromatosis and iron overload syndromes.

A comparative study of diagnostic criteria in AOSD by Mason et al suggest the Yamaguchi criteria are superior to the others tested, including Cush et al quoted by Knight and Symmons. However, none of the criteria to aid diagnosis make use of serum ferritin measurement despite the claims for its use in the literature and acceptance in clinical practice. Although undoubtedly useful if very high, it is not clear what the relevance of a normal value in AOSD is, in a case satisfying clinical diagnostic criteria (although we have never seen such a case). In rare diseases such as AOSD, it is difficult to assess and evaluate diagnostic criteria and calculate specificity and specificity of possible disease markers. If serum were stored on this patient it would be interesting to know the serum ferritin measurement and how, if at all, it would have affected this patient’s management.

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Authors’ reply

We thank Drs Quinn and Gough for their interest in our paper. Our patient did have his serum ferritin measured in 1992. It was 197 μg/l (normal range 15–200). This was therefore a situation in which the patient satisfied clinical diagnostic criteria for adult onset Still’s disease (AOSD) but had a normal ferritin concentration. As the authors point out, had the ferritin concentration been high, this would have helped to confirm the diagnosis but given that it was in the normal range, it could not actually be used to refute the diagnosis. It was always felt that this patient’s disease was not typical of AOSD and the various physicians who looked after the patient were always willing to consider alternatives. However, it is difficult, even with the benefit of hindsight, to conclude that Whipple’s disease could have been diagnosed earlier. Although the normal serum ferritin was not in keeping with the diagnosis of AOSD it did not point towards any other diagnosis in particular.

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Ear, ear, what’s going on in Norfolk?

Having recently started work in the rheumatology department of the Norfolk and Norwich Hospital I read with great interest the article on Hugh(h)ears? (ear: an unusual presentation of antiphospholipid syndrome. Ann Rheum Dis 1999;58:65–6.

Authors’ reply

We note with interest the report from Dr Gaffney. While the coincidence is indeed curious, these cases do suggest possible mechanisms for activation of thrombosis. The external ear is characterised particularly by a lower average temperature than core body temperature, and by its susceptibility to trauma and pressure effects. In our case, cryoglobulins were not identified, and no comment in this regard is made by the authors. There is no specific reference to any aural trauma, though presumably, as in our case, it is difficult to assess what pressure was exerted on the external ear during sleep. It is plausible that such pressure causes a degree of blood stasis, which together with inadequate anticoagulation, resulted in thrombosis. Such speculation may be interesting, but it is this latter point that deserves emphasis—patients with antiphospholipid syndrome who have had thrombi will do so again, potentially with serious consequences, if the INR is not scrupulously maintained above 3.0, a message that must be spread widely: “Friends, Norfolk countrymen, lend me your ears!”

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Antinuclear antibodies in relapsing polychondritis

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Ann Rheum Dis 1999 58: 656-657
doi: 10.1136/ard.58.10.656

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