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 polyarthritis, 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 had to be stopped after four months and a total cyclophosphamide dose of 9 g because of an anaphylactic reaction during an infusion. Despite azathioprine, 150 mg/day, and prednisolone, up to 20 mg/day, she developed severe hypertension (210/120 mm Hg) and biopsy confirmed lymphocytic cutaneous vasculitis. Cladribine (0.05 mg/kg/day for seven days as continuous intravenous infusion) and prednisolone 60 mg/day were started. Cutaneous vasculitis resolved within five days and serum creatinine fell from 190 to 120 μmol/l in five weeks. Cladribine was well tolerated apart from a herpes simplex infection in the natal cleft that responded to acyclovir. She relapsed three months later, with a new rise in creatinine (154 μmol/l) and recurrence of cutaneous vasculitis.

A further infusion of cladribine was given, keeping prednisolone at 5 mg/day. Although the vasculitic rash again resolved, renal function and proteinuria continued to deteriorate.

She has subsequently been maintained with mycophenolate mofetil 1 g twice daily and oral prednisolone. Serum creatinine has returned to 98 μmol/l and proteinuria to 5.3 g/24 h and remained stable despite gradual reduction of prednisolone dose to 15 mg daily.

CASE 2

A 35 year old woman was diagnosed with SLE at age 31, with fever, pancytopenia, and nephrotic syndrome (proteinuria 6.65 g/24 h). ANA and anti-dsDNA antibodies were present. Renal biopsy revealed WHO Class III lupus nephritis. In the next four years she required three treatment cycles of intravenous cyclophosphamide (total dose per six month cycle: 9–10 g). Azathioprine, methotrexate, cyclosporin A and prednisolone 5–40 mg/day 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.

In the initial study by Davis *et al*,[1] three of seven patients treated with continuous cladribine infusion for a week responded completely and renal function did not deteriorate in any of the seven patients. Our limited experience suggests that cladribine may be effective in other manifestations of SLE (that is, cutaneous vasculitis), but it does not seem to have a consistent effect in severe nephritis. Good tolerability of the drug was confirmed and although herpes simplex infections occurred in both patients the role of corticosteroids cannot be ignored.

Further studies are required to establish the position of cladribine in the treatment of SLE especially in the presence of other lymphocyte depleting agents such as mycophenolate mofetil, which is reported to be effective in lupus nephritis,[2–4] even in cases refractory to cyclophosphamide.[5]

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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,[1] and in successful renal transplantation other complications may ensue, particularly avascular necrosis.[2] 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.[3–6]

Tacrolimus is a novel macrolide with potent immunosuppressive effects and with a very similar mechanism of action to cyclosporine A—that is, calcineurin phosphatase inhibition.[7 8] 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

	Patient 1				*Patient 2*	
	First infusion		*Second infusion*			
	Before	*After*	*Before*	*After*	*Before*	*After*
Proteinuria	12.25 g/24 h	4.2 g/24 h	5.2 g/24 h	12.4 g/24 h	4 g/24 h	7.2 g/24 h
Serum creatinine	190 μmol/l	120 μmol/l	154 μmol/l	163 μmol/l	149 μmol/l	243 μmol/l
Anti-ds DNA	132 IU/ml	58 IU/ml	292 IU/ml	>300 IU/ml	171 IU/ml	49 IU/ml
C3	0.51 g/l	0.67 g/l	0.72 g/l	0.51 g/l	0.39 g/l	0.60 g/l
C4	0.13 g/l	0.14 g/l	0.15 g/l	0.12 g/l	0.12 g/l	0.16 g/l
C3d	22 units/ml	10 units/ml	23 units/ml	20 units/ml	13 units/ml	12 units/ml
Urine analysis	red cells, hyalogranular, cellular casts				red cells, a few casts	

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.

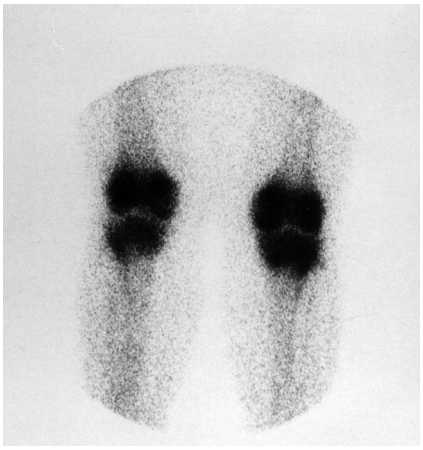

Figure 1 Bone scintigraphy, showing increased uptake in both knees.

or increased temperature. She had no signs of autonomic vasomotor disturbances and articular 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 100 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 (5.1 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.[4–6] 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 uncomplicated RSDS has been demonstrated,[4 5] so 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 tacrolimus 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.[10] However, there are reports that calcium channel blockers (albeit of the dihydropyridine type) can improve the bone pain syndrome.[11]

Although leg bone pain syndrome in kidney transplant patients who have received cyclosporin A is very rare, there are case reports described in the literature.[4–6] To our knowledge, this is the first case of a renal transplant patient with pain in the lower limbs, related to tacrolimus treatment. Additional case reports are needed to support this association.

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Spleen haemorrhagic infarction and hazards of anticoagulation in Wegener's granulomatosis

In the largest cohort published to date, no splenic involvement is described in Wegener's granulomatosis (WG).[1] We report on two patients who required splenectomy for symptomatic spleen infarction in the course of WG.

CASE 1

A 42 year old man was admitted with an eight month history of arthritis and lower limb dysesthesia. Examination showed an acutely ill patient with a 39°C fever, oral ulcers, haemorrhagic gingival hyperplasia, bilateral haemorrhagic nasal discharge with crusts, diffuse necrotic purpura, neuritis, and black discoloration of some fingers and toes. The spleen was not palpable. Silent anterior myocardial infarction was diagnosed because of raised MB-CK levels and ST-segment increase with loss of R waves in leads V1,V2,V3 on electrocardiogram.[2] Antineutrophil cytoplasmic antibodies (c-ANCA) were disclosed in serum and necrotising vasculitis was shown on skin biopsy specimen.[3] No antiphospholipid antibody or coagulation protein abnormality could be disclosed. Treatment consisted of intravenous administration of prednisolone, cyclophosphamide, sodium heparinate, diltiazem, dinitrosorbide and enalapril. His short-term course was uneventful. At day 14, the patient suddenly developed a severe haemorrhagic shock. Echotomography of the abdomen showed a splenic mass. At laparotomy, the spleen was almost disrupted by voluminous haematoma. Histological analysis of the spleen showed widespread necrotising vasculitis with haemorrhagic infarction. After five years of follow up, the patient is in complete remission with oral cotrimoxazole treatment.

CASE 2

A 23 year old young man was admitted in August 1996 because of repeated otitis media, sinusitis, epistaxis, headache, arthralgia with fever and weight loss. Despite a short course of oral corticosteroids and antibiotics, his general condition worsened. Antiproteinase 3 c-ANCA were disclosed in serum. Chest computed tomography showed pulmonary nodules. Intranasal endoscopic biopsies demonstrated necrotising vasculitis with epithelioid and giant cells. Treatment included oral prednisone and intravenous cyclophosphamide pulses. After a few days, serum creatinine concentrations abruptly increased to 198 µmol/l and urine analysis showed microscopic haematuria and proteinuria. High dose methylprednisolone pulses were then given, intravenous cyclophosphamide was changed to a 100 mg oral daily regimen and the patient eventually achieved remission. In October 1996, abdomen computed tomography showed an intrasplenic lesion that was consistent either with a splenic infarct or haematoma (fig 1). The later course was marked by a WG flare in January 1997, which was complicated with massive thrombosis of the left iliofemoral vein and the inferior vena cava. No thrombophilic disorder could be found. Intravenous heparin then oral anticoagulation with acenocoumarol were given. Because of persistent left hypocondrium tenderness, splenectomy was performed in September 1997. Histological examination showed spleen infarction with organised haematoma and sequelae of vasculitis (fig 2).

COMMENT

Because they are vessels without collateral flow, occlusion of distal parenchymal splenic arteries leads invariably to splenic infarction. Of note, two of the three patients described by Wegener in 1936 had spleen involvement.[4] The frequency of spleen involvement ranges from 50% to 100% of WG cases at necropsy.[5–7] Histological data frequently