our institute. Five cases developed pulmonary complications. Four of five cases involved pleuritis and one was eosinophilic pneumonia. All cases were treated with predonisolone with or without immunosuppressive drugs. There were no previous cases of interstitial pneumonia.

Corbett *et al*. (6) reported a case of chronic persistant interstitial pneumonia in 1983. Van Hoeyweghen *et al*. (7) described a case showing basal lobe infiltrates. Lung biopsy showed patchy interstitial fibrosis and chronic inflammation. Pouchot *et al*. (8) reported one patient who developed a pleural effusion, pericarditis, and interstitial pneumonia, which into an acute respiratory distress syndrome and required mechanical ventilation. Stoica *et al*. (9) also reported a case of ASOD that was associated with severe respiratory failure.

KL-6 is a high-molecular-weight glycoprotein and is classified as "Cluster 9 (MUC1)" (10). KL-6 is a chemotactic factor for most fibroblasts and the increased level of KL-6 in epithelial lining fluid in small airways may cause intra-alveolar fibrosis in fibrosing lung diseases. Circulating KL-6 has been shown to be a sensitive marker indicating disease activity of interstitial pneumonia. In this case, even though ferritin and C-reactive protein were decreased after predonisolone therapy, interstitial pneumonia worsened. KL-6 reflects lung involvement more sensitively. Lung involvement of AOSD may progress to severe respiratory failure (10). Thus, monitoring KL-6 may be useful for a better estimation of prognosis.

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Maternal and fetal outcome of pamidronate treatment before conception: a case report

Sirs,

Idiopathic hyperphosphatasia is a genetic bone disorder and is accompanied by very high bone turnover and progressive bone deformity (1).

Pamidronate therapy appears to be promising for patients with idiopathic hyperphosphatasia. Bisphosphonates have been shown to cross the placenta in humans (2). Animal studies have shown that this drug during pregnancy can result in shortening of diaphyseal bone, increased diaphyseal trabecular volume, and a reduction in bone marrow volume in the fetus (2). In view of these observations, the use of bisphosphonates during pregnancy is not recommended.

We present a case of a woman with hereditary hyperphosphatasia who had received pamidronate before conception. A 30-year-old woman with idiopathic hyperphosphatasia had been treated with cyclical intravenous pamidronate for 42 months in order to prevent the development of skeletal deformity and disability. Pamidronate was given at a dose of 1 mg/kg on three consecutive days every four months, total cumulative pamidronate dose of 9 mg/kg/year.

The woman conceived one month after the last cycle. No further pamidronate was given during pregnancy. The patient received daily doses of 1000 mg elemental calcium and no vitamin D. All prenatal exams were normal. After 36 weeks of gestation, premature membrane rupture occurred and a female infant was born, with Apgar scores 8/9 and birth weight was 3130 g. The maternal serum ionized calcium, phosphate, alkaline phosphatase, and parathyroid hormone (PTH) concentrations were within reference limits during pregnancy (1.20 mM, 1.42 mM, 102 U/L, and 5.4 pM, respectively), as well as 24 h after delivery (1.16 mM, 1.12 mM, 118 U/L, and 3.1 pM, respectively).

No neonatal dysmorphic features, fractures, or long bone deformities were noted at birth. At 6 and 24 h of age, the child had normal serum ionized calcium, phosphate and PTH concentrations (1.08 mM, 1.39 mM, and 4.6 pM, respectively, at 24 h). She was asymptomatic at that time and there were no signs or symptoms suggesting hypocalcemia as indicated by normal breast-feeding and the lack of irritability, jitteriness, tremors and muscle twitching. There was no clinical evidence of cardiac rhythm disturbances. The mother and her child were discharged from the hospital 60 h after delivery.

Breast-feeding was maintained and the newborn had an uneventful postnatal period. Both mother and child were examined 14 days after delivery and the cardiovascular, respiratory, gastrointestinal, and neurological systems were found to be normal upon clinical examination. Serum biochemical analysis was also normal.

During the third trimester of pregnancy, fetal calcium requirements may exceed maternal intestinal absorption, a fact resulting in the resorption of calcium from the maternal skeleton (3). Previous maternal pamidronate administration might therefore reduce the amount of skeletal-derived calcium that is available for fetal bone mineral accumulation.

The pamidronate administration during pregnancy in animals showed that toxicity, embryo lethality or severe underdevelopment and a marked skeletal retardation of the fetuses were only observed at doses about ten times higher than the human therapeutic dose (2, 4).

Two case reports have been published on pregnant women who received bisphosphonates for malignant hypercalcemia (5, 6) and the infants developed hypocalcemia. Munns et al. published the first report on maternal and fetal outcomes after pamidronate therapy before conception. Two mothers had osteogenesis imperfecta and the pregnancies were uneventful (7).

Bisphosphonates are known to persist in mineralized bone for many years and the fetus may still be exposed to bisphosphonates (2). It is also conceivable that the suppressed bone turnover might result in maternal complications during pregnancy or lactation.

In conclusion, the present case does not provide evidence that maternal health is affected during pregnancy by pamidronate treatment administered before conception. However, the occurrence of adverse events (hypocalcemia, hypercalcemia) during pregnancy or after delivery cannot be ruled out; mother, fetus and newborn should be followed up carefully throughout these periods.

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Early onset neutropenia after rituximab in lupus nephritis

Sirs,

Rituximab is a mouse/human chimaeric IgG1-k monoclonal antibody that targets the CD20 antigen found on B-lymphocytes. It may be an effective treatment for patients with systemic lupus erithematosus (SLE) (1, 2). In this report we describe a case of early onset neutropenia after rituximab therapy in SLE.

A 48-year-old Caucasian woman was diagnosed, ten years ago, as having SLE and diffuse proliferative glomerulonephritis (class IV) with nephrotic syndrome. Remission of the nephropathy was achieved with steroids and cyclophosphamide.

New onset polyarthritis appeared three months before her current admission. On physical examination the blood pressure was 160/100 mm Hg and mouth ulcers were noted. Laboratory studies: hemoglobin 9.5 g/dl, white blood cell count 5.76 109/l (nv 4,00-11,00), neutrophils 4.45 109/l (nv 2.00-7.20), lymphocytes 0.76 109/l, platelets 118 109/l, creatinine 1.2 mg/dl, C3 52 mg/l, C4 6 mg/dl, ANA 1/640, anti-DNA 1/320; lupus anticoagulant, anticardiolipin antibodies, cryoglobulins and c-reactive protein were negative or normal.

HbsAg was negative and anti-HBsAc was positive. Anti-HBcAc negative for IgM and positive for IgG, anti-HCV negative. 24-h proteinuria was 2.6g /24h, urinary sediment: microhematuria and red blood cell casts. The urine culture was sterile. The echocardiography and abdominal ultrasound were normal. A lupus flare was diagnosed with probable lupus nephritis relapse. She was treated with three pulses of methylprenisolone (0.5 g each), following prednisone 0.5 mg/kg/day po, and three monthly infusions of cyclophosphamide. However, the serum creatinine worsened to 5 mg/dl. A kidney biopsy had to be cancelled due to prolonged bleeding time not corrected after desmopressin therapy. ANCAs (PR-3, MPO) and anti-glomerular basement membrane antibodies were negative; magnetic resonance imaging of the renal arteries and veins was normal. Rituximab therapy was started at a dose of 700 mg (375 mg/m2); previous white blood cell count and neutrophils were normal. Five days after rituximab therapy, white blood cell count was 3.75 109/l with 3,33 109/l neutrophils. In three days, the white blood cell count normalized. Two weeks later, a second dose of rituximab was administered; 24 hours after it the white blood cell count fell to 2.39 109/l with 1.66 109/l neutrophils; the hemoglobin and platelets did not decrease. One day later, she presented a body temperature of 38ºC. Granulocyte colony-stimulating factor (GCSF), broad-spectrum antibiotics and fluconazole were given. Blood and urine cultures, skin tuberculin test, and serology for infectious agents were negative. Neutrophil-bound antibodies (IgG and IgM, flow cytometry) were negative. The nadir of leukocytes, 1.31 109/l with 0.85 109/l neutrophils, was reached five days after rituximab and three days after starting GCSF; afterwards they normalized in one week. The patient became afebrile and made and uneventful recovery. Bone marrow aspiration disclosed normal granulopoiesis, no maturation arrest and neutrophil precursors present. Her renal function worsened and hemodialysis was started.

Rituximab may be a valuable treatment for lupus nephritis refractory to cyclophosphamide (3, 4). In the oncological setting, several cases of late-onset neutropenia have been described. It tends to occur 2-6 months after rituximab single therapy and can be associated with serious infections (5). Because CD20 antigen is not present on neutrophils, this complication has been related to autoantibodies against neutrophils during immune reconstitution. Neutropenia resolved spontaneously or responded to G-CSF and/or intravenous immunoglobulin treatment (6).

The incidence of neutropenia appears to be rare in patients with SLE treated with rituximab (2, 7). However, recently two cases of early-onset neutropenia associated with rituximab for SLE have been reported (8). In our patient, there was a close temporal correlation between drug exposure and the early-onset neutropenia. After the first dose of rituximab, we observed a mild decrease in white blood cell count and neutrophil values. On re-exposure, the patient developed a severe neutropenia. The early-onset of the adverse reaction would suggest an immune mediated mechanism (9). Afterwards, she presented fever; apparently the infection was secondary to neutropenia but the reverse cannot be ruled out.

This case report illustrates the necessity to carry out a close monitoring of neutrophil count during rituximab therapy.

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