LETTERS TO THE EDITOR

Failure of First-Line Therapy with Intravenous Immunoglobulin in a Child with Scleromyositis

Sir—We present a 9-yr-old Caucasian girl who was referred with a 4-month history of slowly progressing reddening of the toes and medial malleoli, insidious development of dry and scaling erythema on knees and elbows, progressive erythematous rash on knuckles and palms with cracks, bleeding and desquamation of the skin, facial pallor, coldness and stiffness of hands, and irritating tingling of hands and feet during the night, as well as fatigue and malaise. Two years previously, she had complaints of visual disturbance when chronic bilateral anterior uveitis had been diagnosed associated with HLA A2, 10, B8, 18; DR3 tissue type and an antinuclear factor (ANF) titre of 1:80, but negative antibodies to double-stranded DNA (ds-DNA). She was treated with topical corticosteroid and mydriatic eye drops, the clinical follow-up was unremarkable and a year later the ANF titre was still 1:50, but antibodies to extractable nuclear antigens (ENA) were negative. At presentation to us, her weight was on the 25th centile and height on the 50th centile; facial pallor was striking with dry flaking violaceous rash over the upper eyelids, the skin over the palmar aspect of the fingers was thickened, red and contracted, perungual telangiectasia was evident with an erythematous rash over the dorsum of the metacarpophalangeal and interphalangeal joints (Gottron sign), over the extensor surface of the knees, elbows and the nape of the neck, toes and both malleoli. The skin felt 'waxy' over the forearm and she was unable to straighten her fingers properly (sclerodactyly). There was mild weakness (MRC grade 4+) of neck flexion and of the deltoids, triceps and biceps, and her gait was laboured, especially in trying to run or climb stairs. She had no uveitis and her cardiological evaluation including echocardiography was normal. Pulmonary function tests revealed reduction of vital capacity (FEV1, 61% and FVC 67% of predicted values). Laboratory investigation showed an elevated creatine kinase (CK) at 2372 U/l (normal < 140), rheumatoid factor (RF) titre of > 1:640, antinuclear antibody (ANA) titre of 1:640 with a nucleolar pattern of staining and subsequently antibodies to PM-Scl were found to be positive. The remainder of the autoantibody screen, C3, C4 and immunoglobulin concentrations, C3d and anticardiolipin antibodies, CRP, as well as her blood count, Coombs test, viral serology and routine biochemistry were all normal. Skin biopsy showed a mild perivascular lymphocyte infiltration, but no vasculitis; immunohistochemistry revealed granular deposits of IgA, IgM and C3 along the dermoepidermal junction as well as trace deposits of C3 on the dermal vessels. Muscle biopsy showed severe inflammatory changes, with muscle necrosis, regeneration and atrophy, but no clear-cut perifascicular fibre atrophy. She was treated initially with high-dose IVIG (Sandoglobulin 2 g/kg/day). Within 24 h of her first infusion, she developed fever, vomiting, headache and neck stiffness, and a lumbar puncture revealed turbid cerebrospinal fluid (CSF) containing 2500 white cells (96% polymorphonuclears), raised protein at 2.65 g/l (normal <0.4) and low glucose at 1.1 mmol/l (normal 2.2-4.4) so that she was commenced on dexamethasone and cefotaxime. Prolonged culture of the CSF proved to be negative for both bacteria and viruses; she made a good and rapid recovery, and a presumptive diagnosis of aseptic meningitis as a complication of IVIG was made. The same dose of IVIG was repeated after 3 weeks, but over 2 days without complications. The rash had initially improved somewhat, and the CK level had fallen (1464 U/l), but as after 2 months there was no further improvement, prednisolone 2 mg/kg/day was commenced and continued for 6 weeks. Thereafter, monthly IVIG (1 g/kg) was continued over the next 5 months, whilst the prednisolone was reduced to 1 mg/kg/day and further tapered to an alternate-day maintenance regime (0.25 mg/kg/day) over the next 24 months. Combined with physiotherapy, this treatment dramatically improved her skin rash and muscle strength, as well as her respiratory function (FEV1, 81% and FVC 83% of predicted) and the serum CK fell to normal levels. She had been transiently cushingoid and recently had a low-grade recurrence of anterior uveitis needing topical steroids, but at present she is leading a completely normal and very active life.

The initial diagnosis of an overlap syndrome [1] with prominent features of juvenile dermatomyositis (DM) [2] was confirmed to be that of childhood scleromyositis [3] when antibodies specific to the PM-Scl nucleolar antigen were detected [4, 5]. The original presentation with chronic anterior uveitis has not been previously associated with this disease entity [3-5]. The myopathy of scleromyositis is indistinguishable from that of DM [6], and the prognosis is generally favourable with corticosteroid treatment [3]. Several uncontrolled trials suggested a beneficial role for IVIG in the therapy of inflammatory myopathies, including scleromyositis [7, 8]. IVIG seems less effective as a first-line treatment in patients with chronic, refractory disease and better results were obtained when used in association with steroids [8]. Children with refractory DM showed an inconsistent and unpredictable response to IVIG used when conventional treatment failed or when this, principally corticosteroids, caused severe side-effects [9]. However, as the only controlled
trial of IVIG treatment demonstrated clinical improvement in 9/12 patients with refractory DM [10], we decided to use IVIG as a first-line treatment to try to avoid the well-known serious side-effects of high-dose corticosteroids. Generally, complications of IVIG are thought to be rare [11], but the inflammatory reaction of unknown nature presenting as aseptic meningitis, as happened with our patient, has been reported on a number of occasions [12].

The first-line treatment with IVIG in our patient, who had corticosteroid-responsive disease, was ineffective. Although it has been recently shown that IVIG could prevent the major pathogenic event in DM by modulating the complement-mediated destruction of microvasculature [13], the inconsistent benefit of IVIG treatment in inflammatory myopathies is probably related to the heterogeneity of the disease and different underlying immunological aberrations [6–10, 14].

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Methotrexate Treatment Every Other Week in Patients with Juvenile Chronic Arthritis

Sir—Low-dose weekly methotrexate has been shown to be an effective treatment for patients with juvenile chronic arthritis (JCA) [1]; however, its long-term toxicity is not well known, and it is also unclear when the drug should be stopped after remission is achieved. Methotrexate is usually given once a week, even if this interval schedule has never been proven to be optimal; two studies [2, 3] have shown that some adult patients with RA with stable disease activity can be switched from a weekly to an every-other-week regimen without major flares. Since 1992, we have started to switch some patients who responded to methotrexate treatment (at least 50% reduction of ESR and number of active joints) to a fortnightly maintenance schedule (keeping the weekly dose stable).

We retrospectively reviewed our data in order to determine whether in those patients methotrexate treatment can be given every other week without diminished efficacy. Twenty-eight patients were responders to methotrexate treatment (given as 10 mg/m² once/week i.m.) using the above criteria; of those, 15 were switched to a maintenance regimen of the same weekly dosage administered every other week. Three patients were affected with systemic-onset JCA, four with extended oligoarticular JCA and eight with polyarticular JCA (one of whom was RF positive). Mean age was 14.8 yr (range 8–22) and mean disease duration prior to methotrexate treatment was 34.4 months (range 8–84).

Clinical and laboratory response was obtained after a mean of 11.2 months (range 6–18). Methotrexate was continued weekly for a mean period of 16 months (range 12–30) prior to switching to the biweekly schedule. Patients were then followed for a mean period of 28 months (range 2–46).

The subsequent course of disease activity and treatment schedules is summarized in Fig. 1. Up to now, four patients had a flare of disease activity (after 2, 4, 16 and 21 months of biweekly administration). The follow-up from the flare of those patients ranges from 0 to 8 months, with a response (after 8 months) only in one patient who had to be started on steroids. In three patients, methotrexate was discontinued while on the biweekly regimen because of sustained (36 and 40 months) remission in two and following major orthopaedic surgery in the third. Two out of three patients flared (after 1 and 3 months off therapy), with subsequent return to the weekly schedule in both and