Active systemic lupus erythematosus successfully treated with Rituximab and oral steroid

Sirs,

Rituximab is an anti-CD 20 monoclonal antibody which has been used to deplete B lymphocytes in non-Hodgkins B cell lymphoma (1), and more recently in autoimmune disease, including SLE. Most workers have included intravenous cyclophosphamide (i.v. CTX) and high dose steroid in their treatment regimens (2), or given Rituximab weekly for at least 4 weeks, some with further infusions at 3 monthly intervals (3, 4). We report 4 SLE patients with active and resistant disease treated successfully with just 2 infusions of Rituximab 2 weeks apart, no i.v. CTX, and only a relatively modest dose of steroid during the treatment period.

Patient one is a 39-year-old male with a 10 year history of SLE, who presented initially with arthritis, leucopenia, elevated anti-ds-DNA antibody and profound thrombocytopenia. Anti-cardiolipin antibody was negative. He had constant haematuria on dipstick urinalysis, and frequent episodes of frank haematuria. He had been unable to use non-steroidal anti-inflammatory drugs for arthritis due to thrombocytopenia, and platelet count had been less than 10×10^6 for more than 3 years, despite aggressive treatment including a course of i.v. CTX and steroid therapy. Immunosuppressive therapy was withdrawn after he developed a life-threatening pneumonia.

After a single dose of 500mg Rituximab the platelet count rose to 86×10^6, and after a second dose 2 weeks later, to 156×10^6. 35mg of oral prednisolone was prescribed from day 1 to day 5, and day 12 to day 17. There was no change in titre of anti-nuclear antibody with treatment, but anti-dsDNA antibody levels fell from 35 IU/l before Rituximab to 10 IU/l after the second treatment (0-35), and levels of C_3 and C_4 rose slightly (0.74g/l to 0.93g/l, 0.13g/l to 0.19g/l) after treatment.

Six months after treatment his platelet count remains $>100 \times 10^6$, and he is taking no immunosuppressive or prednisolone therapy. He has had neither dipstick nor frank haematuria since the second infusion, and he has no symptoms or signs of arthritis.

Patient two is a 46-year-old female with a 15-year-history of SLE. She presented initially with arthritis, lymphopenia and photosensitive rash, and was found to be positive for anti-nuclear antibody (ANA), anti-Ro antibody and anti-La antibody. More recently she developed a florid vasculitic rash associated with severe unremitting headache and depression. ESR was elevated at 56 mm/hr, CRP undetectable, anti-cardiolipin antibody negative, anti-dsDNA antibody 35 IU/ml (0-35), ANA titre 1 in 320. MRI of brain revealed 2 small nodular lesions in the sub-cortical white matter of the frontal lobe, in keeping with the sub-cortical infarcts seen in cerebral vasculitis. The findings were confirmed on PET scan of brain.

Her symptoms were unchanged despite 6 infusions of i.v. CTX 750mg and methylprednisolone over 6 months. There was however a profound response in terms of rash, headache and affect after 2 doses of 500mg Rituximab 2 weeks apart, which lasted for over 9 months, during which time she remained on a varying low dose of steroid (< 10 mg prednisolone). 35mg of oral prednisolone was given at the time of infusion as outlined under patient one (above).

ANAtitre fell to 1 in 40 after the Rituximab treatment, anti-dsDNA antibody to within normal limits, ESR to 20mm/hr and CRP remained unchanged. C_3 rose from 0.93g/l before to 1.13g/l after Rituximab treatment, and C_4 from 0.16g/l to 0.20g/l. She received a further infusion of 500mg Rituximab one year after the first dose when her headache returned, with an increase to 25mg prednisolone daily during and after treatment. MRI findings were unchanged. On this occasion there was a considerable improvement in headache, but not complete resolution.

Patient three is a 54-year-old female with a 27-year history of SLE. She developed increasingly severe headache and decline in cognitive function over 6 months, and then focal seizures associated with intermittent hemiplegia. She received 6 infusions of CTX and methylprednisolone over a 10-month period, during which time the frequency of her seizures increased to up to 10 a day, unresponsive to anti-epileptic medication. MRI scan of brain showed subcortical infarcts not seen in a scan performed 3 years previously, suggestive of ongoing vasculitis. EEG was unremarkable. Anticardiolipin antibody titre had been elevated in the past, but not for several years before this presentation.

Two infusions of Rituximab 500mg were given with a 2-week interval. 30mg prednisolone was given from day 1 to day 5 and, day 12 to day 17 with maintenance of 10mg prednisolone continued after Rituximab.

Anti-dsDNA antibody fell from 40 IU/l to 17 IU/l (0-35) after the second infusion, and haemoglobin rose from 10.5 g/dl to 11.7 g/dl. CRP remained undetectable. There was no significant change in levels of complement or immunoglobulin, which remained within normal limits.

Headache improved within a few days of the first treatment, and within a few weeks of the second infusion there were no further seizures or hemiplegia. Formal neuropsychological assessment was repeated 3 months after therapy, and showed a considerable improvement, and she has remained asymptomatic for 8 months.

Patient four is a 31-year-old female with a 7 year history of SLE, characterized by arthritis, nephrotic syndrome and steady decline in renal function. Lupus nephritis was unresponsive to methylprednisolone and CTX infusions over a 6-month period, mycophenolate mofetil and very high dose oral steroid.

Two infusions of Rituximab 500mg were given with a 2-week interval. 1g methylprednisolone was given the day before Rituximab. Oral maintenance therapy of 80mg prednisolone and 100mg CTX was continued. Before Rituximab, urinalysis showed blood ++++, protein +++ (4.12g/24hr), serum urea 17.1mmol/l, (2.5-6.8) serum creatinine 107 mmol/l (54-100), creatinine clearance 59.8 ml/min (85-125), serum albumin 27 g/l (35-50).

3 months after Rituximab urinalysis showed blood trace, protein trace (0.21g/24hr), serum urea 5.3 mmol/l, serum creatinine 76 mmol/l, creatinine clearance 109 ml/min, serum albumin 34 g/l (35-50). C_3 rose from 0.36g/l to 1.06g/l, C_4 from 0.04g/l to 0.18 g/l, anti-dsDNA antibody fell from >200 IU/ml to 23 IU/ml, ANAtitre from 1 in 160 to 1 in 40.

Almost 12 months after treatment, all her indices of renal function and lupus activity have remained stable or continued to improve on maintenance therapy of just low dose oral steroid, and her dramatically cushingoid appearance has entirely resolved.

Rituximab is chimeric human/murine anti-CD20 monoclonal antibody, and was first described in the treatment of resistant non-Hodgkin's B cell lymphoma 7 years ago (1), and subsequently in the treatment of a range of other B cell malignancies. A small number of reports now describe its use in SLE, both individual case reports (5) and in short series.

Leandro *et al.* treated 6 female SLE patients with 2 doses of 500mg Rituximab 2 weeks apart, but with the addition of 750mg CTX with each dose and high dose oral steroid. Five out of 6 patients showed global improvement, particularly in terms of renal function (2). Weide and colleagues used 4 infusions at weekly intervals in 2 patients, repeating the treatment every 3 or 6 months, also with improvement (3), and Kneitz produced benefit in 3 out of 4 patients with SLE and thrombocytopenia (6) , and also showed effective B cell depletion for 8 to 12 months.

Leandro, Edwards and Cambridge included CTX infusions in 4 out of 5 of their cohorts in their dose response study in rheumatoid arthritis, and suggested that only in protocols including CTX could major improvement be expected. Almost all of their patients also received much higher doses of Rituximab than we report in this series (7).

In our SLE patients we attempted to minimize the side-effects associated with the profound immunosuppression seen in regimens similar to those for the treatment of B cell lymphoma, and those specifically asso-

ciated with CTX treatment, by using modest doses of Rituximab and steroid and avoiding the use of i.v. CTX. We found this regimen to produce a significant and sustained response in all 4 of the patients studied.

In 4 SLE patients with a spectrum of presentations, including those with cerebral lupus, even a relatively low dose of Rituximab and steroid may induce prolonged remission in active disease resistant to aggressive therapy including i.v. CTX.

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Diacerein has a structure/ disease-modifying effect on hip osteoarthritis

Sirs,

We read with great interest the discussion in the Evidence-Based Rheumatology section of a recent issue of this journal (1) regarding the results of the ECHODIAH trial and the structure-modifying effects of diacerein in hip osteoarthritis (2).

In this discussion, the evidence generated by the 3-year ECHODIAH trial conducted on 507 patients suffering from hip osteoarthritis (OA) was reviewed. The results of the trial demonstrated the structure-modifying effects of diacerein in hip OA; at the end of the trial the progression of joint space narrowing (JSN), as defined by a loss of joint space width (JSW) of ≥ 0.5 mm, was significantly smaller in the patients receiving diacerein than in those receiving placebo, both in the intent-to-treat population (50.7% versus 60.4%, p = 0.036) and in the completer analysis (47.3% versus 62.3%, p = 0.007). Diacerein had no apparent effect on the symptoms of OA in this trial; nevertheless, a post hoc covariate analysis which took into account the use of analgesics and NSAIDs by the patients showed the presence of a significant beneficial effect of diacerein on the symptoms of OA, as measured by the Lequesne index. The safety of the treatment with diacerein was good, and the most frequent adverse events were transient changes in bowel habits.

In addition to the strong evidence provided by the above results, we feel that the concluding sentence of A. Del Rosso's summary of the study results, "... before diacerein can be formally added to the other accepted therapies further investigations are needed ...", does not adequately reflect the position that diacerein occupies among the currently available treatments for OA. Indeed, diacerein has been on the market since 1994 in France, since 1998 in Israel, and thereafter in several other European countries. Thus, we must point out that, contrary to Del Rosso's assumption, diacerein already is an accepted treatment for OA.

Furthermore, we feel that this concluding remark does not adequately reflect the status that diacerein enjoys among the currently available treatments for OA. Indeed, the demonstration of the beneficial effects of diacerein on the progression of JSN in hip OAprovided by the results of ECHODIAH led to an update of the diacerein SmPC by the French Health Agency, with the addition of a new pharmacodynamic property. Therefore, we believe that the concluding remark may be attributed to a misinterpretation of the last sentence in the summary of the article published in *Arthritis and Rheumatism* (2).

Whilst we agree that an understanding of the full clinical relevance of the findings of the ECHODIAH trial may require further investigation, as is often the case in clinical medicine, we strongly believe that the acceptance of diacerein among the recognized treatments for OAdoes not need to be established again.

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Prolonged QTc interval and juvenile dermatomyositis

Sirs,

Cardiac involvement in dermatomyositis was first described in 1899 (1). Once considered uncommon in patients with juvenile dermatomyositis (JDMS), cardiac involvement has been increasingly recognized (2-4). Almost half of the electrocardiogram (ECG) recordings done for patients with definite JDMS show abnormalities at time of disease onset but serious cardiac involvement is rare (5-6). Reported ECG abnormalities include tachyarrhythmias, varying degrees of atrioventricular heart block, ST-T wave changes secondary to myocardial ischemia and abnormal T waves (2, 3, 7-9). Prolonged corrected QT interval (QTc) on ECG, however, has not been previously reported. We report a case of JDMS in a previously healthy 4-year-old Caucasian girl with tachycardia and prolonged QTc interval on several ECGs. This condition improved significantly once the underlying disease was controlled with medications.

This previously healthy 4-year-old Caucasian girl presented after 5 weeks of weakness, myalgias and rash. She had no change in phonation or dysphagia. Previous medical and family history was negative for rheumatic or cardiac diseases. The patient had no history of syncope or seizures. There was no history of sudden death, syncope or cardiac problems on either side of the family. Physical exam revealed classic heliotrope and malar rash, mild periorbital edema, Gottron's sign on the metacarpal joints, elbows and knees, and profound proximal and distal muscle weakness. Muscle strength was graded 2/5 based on the muscle strength scale. Nailfold capillaries showed dropout of capillary end-loops and dilated tortuous capillaries. She had mild respiratory distress. Cardiac exam revealed tachycardia (heart rate of 154 beats/min) but normal heart sounds and no rubs or murmurs. Laboratory evaluation revealed elevated creatine phosphokinase (CPK) at 6838 IU/L(75 – 230 IU/L), elevated MB fraction of 78.1 IU/L (0.0 – 5.0 IU/L), aldolase at 36.3 U/L (1.2 – 8.8 U/L) alanine aminotransferase (ALT) at 781 IU/L and aspartate aminotransferase (AST) at 341 IU/L. T cell flow cytometry revealed percentage of CD19 cells markedly increased at 61% of the absolute lymphocyte count (normal for age is