infective pneumonitis and pleurisy, arthralgia and sinusitis. He responded to methyl prednisolone pulses and prednisolone in increasing doses, and azathioprine.

During the following year he had recurrent red eyes, headaches, cough and breathlessness. An NW scan showed extensive sinus opacification. His status deteriorated and he failed to respond to prednisolone up to 25 mg/day and in turn oral cyclophosphamide, azathioprine and mycophenolate mofetil. C-ANCA was weakly positive and cryoglobulins were negative. His urine sediment showed red blood cells (RBC) and some RBC casts. Renal biopsy showed thin glomerular basement membrane disease with no other glomerular changes or vasculitis. He then worsened and developed pancytopenia: Hb 7.2 g/dl, Wcc 1,000/mm^3, Neu 900/mm^3 and Plt 48,000/mm^3. A nodule on the left forearm showed a granulomatous vasculitis characteristic of Wegener's granulomatosis (4). A bone marrow biopsy and trephine were hypercellular and all three cell lines were represented without granulomata or abnormal infiltrates.

He was started on etanercept (ENBREL®) alone, 25 mg twice a week, and dramatically improved in less than a week; FBC showed: Plt 79,000/mm^3, Wcc 1,900/mm^3, Hb 11.6 g/dl, Neu 1,200/mm^3. Methotrexate, 10mg/week, was then started (5-7). The patient continued on etanercept and methotrexate and is in clinical remission.

We have described here two patients with ANCA associated systemic vasculitis who developed pancytopenia that was apparently related to their disease activity. Neither patient had evidence of splenomegaly, viral infection, haemolysis, immune complex disease or drug toxicity and the bone marrow in each case was hypercellular. The rapid improvement in the peripheral blood count with oral cyclophosphamide or etanercept plus methotrexate strongly supports the idea that the pancytopenia was an autoimmune phenomenon and not related to the previous immunosuppressive therapy.

The second patient experienced a life-threatening relapse despite a variety of immunosuppressive agents, so etanercept was administered with excellent results. Whilst the haematological picture of pancytopenia with normal bone marrow is very well described in SLE, to our knowledge this is the first such report in two patients with ANCA associated vasculitis.

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Successful treatment of chronic fatigue syndrome with midodrine: A pilot study

Sirs,

Systematic review of studies on treatment of chronic fatigue syndrome (CFS) revealed that only cognitive behavior therapy and graded exercise are consistently beneficial (1). Both of these modalities are palliative at best, however. Since dysautonomic cardiovascular reactivity is frequently present in CFS patients (2,3), we hypothesized that therapies directed to improve dysautonomia may also improve the symptom of fatigue. Midodrine HCl, a potent α-1-adrenergic agonist, is efficient in the treatment of dysautonomic syndromes such as orthostatic hypotension, vasovagal syncope and postural tachycardia syndrome (4, 5). We conducted an open study to test whether midodrine treatment could benefit patients with CFS. On review of the MEDLINE database we did not find a study describing midodrine treatment of CFS.

Ten patients with CFS meeting the Centers of Disease Control and Prevention criteria for CFS (6) were enrolled in this study, of whom 3 did not complete the treatment and were excluded from analysis. This group included 4 males and 3 females, their mean age was 27 years (range 16 to 29 years),and the mean duration of CFS was 11 months. The control group of 'non-CFS fatigue' patients had fatigue of similar severity to that of CFS patients, but did not otherwise meet the definition criteria of CFS. There were 2 males and 3 females, with a mean age of 42 years (range 26 to 72 years) and a median illness duration of 13 months. The presence of psychiatric disorders were exclusion criteria in both the patient and control groups (6).

The severity of the fatigue was estimated on a scale of 0 to 33 based on Chalder's fatigue severity questionnaire (7). The cardiovascular reactivity was evaluated according to the results of a 10-minute supine/30 minute head-up tilt test (HUTT) (8). Dysautonomic reactivity was recognized either when orthostatic hypotension, vasodepressor reaction,a cardioinhibitory reaction, or postural tachycardia syndrome occurred on tilt, or when a hemodynamic instability score (HIS) > -0.98 was found. The HIS was calculated according to a method recently described by us (8). HIS values >-0.98 strongly correlated with a distinctive cardiovascular reactivity in CFS, with 90.3% sensitivity and 84.5% specificity (8-10).

The patients were off medications for at least two weeks before entering the study. Midodrine treatment was started, p.o. 2.5 mg twice daily in patients and controls. Two weeks later, the HUTT was repeated. When

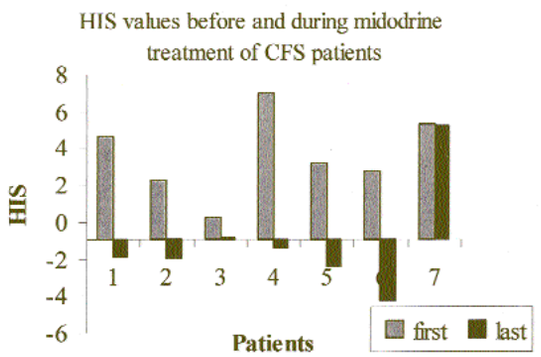

Fig. 1. HIS values before and during midodrine treatment of patients with CFS. Normalization of the HIS occurred in 6/7 patients.

the cardiovascular reactivity returned to normal, the dose of midodrine remained unchanged. When the cardiovascular reactivity continued to be abnormal, the midodrine dose was increased to 5 mg twice daily. Clinical visits were scheduled at intervals of 2 months. On each visit, the fatigue severity score and HIS were determined. After 3 months of treatment the medication was discontinued if no improvement of fatigue was observed. Otherwise, treatment was continued for 6 months or longer.

At entrance to the study, the fatigue severity scores were similar in patients and controls: mean 16 (range 9 to 20) in CFS and mean 17 (range 10 - 21) in controls, while the HIS values differed: mean +4.8 (range +2.28 to +7.03) in CFS and mean –1.69 (range –1.34 to –3.2) in controls. At 3 months of midodrine treatment, the HIS had returned to normal in 6 CFS patients; the fatigue score improved 4 to 8 weeks later. Among the 'responders', 2 patients discontinued midodrine following 6 months and one patient following 12 months of treatment. The fourth patient had recurrence of fatigue and dysautonomic reactivity (HIS = +8.02) after termination of midodrine treatment, but improved soon after reinstitution of midodrine. Two patients preferred not to discontinue treatment and are taking midodrine after 12 and 10 months, respectively. All patients feel much improved. The seventh patient failed to improve on midodrine. As expected, control patients, having no evidence of an abnormal cardiovascular reactivity, did not show any improvement in the HIS and fatigue score.

Midodrine treatment, directed at the autonomic nervous system in CFS, results first in correction of dysautonomia followed by improvement of fatigue. This finding implies that dysautonomia is pivotal in the pathophysiology CFS, at least in a large proportion the patients, and that manipulating the autonomic nervous system may be effective in the treatment of CFS when the presence of dysautonomia has been demonstrated. The combined utilization of the fatigue severity score and the HIS provides complementary information that is useful for monitoring the course of CFS as well as a measure of response to treatment. The results of this preliminary study are encouraging.

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