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Peripheral neuropathy: an unwanted effect of leflunomide?

SIR, Leflunomide (Arava; Aventis Pharmaceuticals, West Malling, Kent, UK) is a new disease-modifying drug licensed for the treatment of rheumatoid arthritis (RA). This isoxazole derivative is a prodrug for the active metabolite A77 1726, which has immunosuppressive properties [1]. Four large randomized control trials have shown good efficacy and safety compared with sulphasalazine and methotrexate. We report two cases of peripheral neuropathy associated with leflunomide.

A 76-yr-old man with an 18-month history of seropositive RA, as yet non-erosive, presenting with polymyalgic symptoms, was treated with corticosteroids and azathioprine, but the latter was discontinued after a rise in aspartate transaminase. He had chronic emphysema and pulmonary fibrosis, which may have preceded the onset of RA, so leflunomide was introduced in preference to methotrexate at a loading dose of 100 mg for three consecutive days followed by a maintenance dose of 10 mg per day. Two weeks later he developed a sensory neuropathy with a stocking distribution up to the malleoli. Leflunomide was discontinued 4 weeks thereafter at follow-up. During this time the patient had also been taking prednisolone, tramadol, Didronel PMO (disodium etidronate), indoramin and celecoxib, none of which is known to cause neuropathy. Glucose, vitamin B12, serum folate, thyroid function, serum protein, Bence Jones protein electrophoresis, cryoglobulins, antineutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA), the Venereal Disease Research Laboratory (VDRL) test and hepatitis B and C serology were all normal or negative. Nerve conduction findings were consistent with motor sensory axonal peripheral neuropathy of the lower limbs. On review 3 months after withdrawal of treatment, there was a clear subjective and objective improvement of the neuropathy, confirmed by repeat nerve conduction studies.

A 69-yr-old woman with seropositive erosive RA of 10 yr duration, previously treated with gold salts followed by methotrexate, was started on leflunomide by the above regime. Three months later she reported numbness in the fingertips and feet bilaterally, with clinical findings compatible with a glove-and-stocking sensory neuropathy involving all fingertips and extending to mid-shins. Leflunomide was stopped. Other medications comprised prednisolone, lansoprazole, simvastatin, losartan and amiodarone, which the patient had been taking for a long period without side-effects. Screening tests for neuropathy, including glucose, vitamin B12, serum folate, thyroid function, serum protein, Bence Jones protein electrophoresis, cryoglobulins, ANCA, ANA, the VDRL test and hepatitis B and C serology, were again normal or negative. No cord or nerve root compression was found on magnetic resonance imaging of the cervical spine. Nerve conduction studies confirmed a sensory motor peripheral neuropathy. Similarly, 3 months after discontinuation

of treatment the patient reported marked improvement in her symptoms, and this was confirmed on clinical examination and repeat nerve conduction studies.

In both our patients there was a tight temporal relationship between the onset of neurological symptoms and the use of leflunomide, strongly suggesting a causative link. This is supported by the documented improvement in neuropathy after withdrawal of leflunomide, while all drug therapy, including the dose of corticosteroids, was unchanged. We acknowledge that sensory polyneuropathy is a recognized extra-articular manifestation of RA. Neither of our patients had a history of rheumatoid nodules and one was non-erosive. The onset of their neuropathy was during a period of improved disease control (Fig. 1), making an association with RA less likely.

The side-effects most commonly reported during drug trials included gastrointestinal symptoms, rash/allergic reactions and alopecia [2–5]. More serious side-effects, such as liver toxicity, agranulocytosis and anaphylaxis, were rare. No cases of peripheral neuropathy were noted during the clinical trials, whilst paraesthesia was an observed adverse event with an incidence of $<5\%$. In both our cases, a yellow card was submitted to the Committee on the Safety of Medicine. The mechanisms by which leflunomide may cause neuropathy are a matter for speculation. One explanation is that the drug triggers vasculitis, which leads to the neuropathy. In this respect a sural nerve biopsy could be useful in future cases.

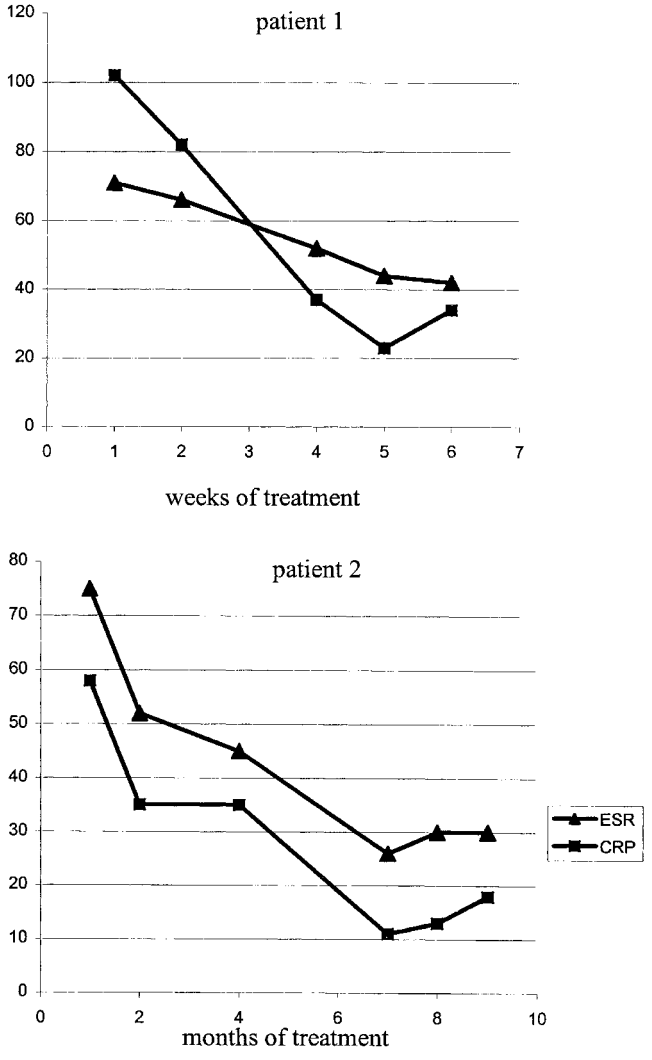

FIG. 1. Changes in erythrocyte sedimentation rate (mm/h) and C-reactive protein concentration (mg/ml) in the two patients.

Leflunomide is a welcome new agent for the treatment of RA as it is as effective as methotrexate [5]. It has a good safety profile according to the experience during the first trials, but with increased clinical use more adverse events may be noted. In particular, rheumatologists should be aware that leflunomide can cause a reversible neuropathy. This is an important side-effect as it causes significant disability in patients already disabled by their disease.

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