# Neuropathy associated with leflunomide: a case series

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Leflunomide is a new disease modifying drug (DMARD) recently licensed for treatment of rheumatoid arthritis. This isoxazole derivative is a prodrug for the active metabolite A77 1726, which has immunosuppressive properties. Leflunomide is now part of the therapeutic arsenal presently available for rheumatic disease, and its safety profile has been assessed by clinical trials[1–3] and extended clinical trials.[4–7] Among adverse peripheral nervous events, only paraesthesia has been reported. Nevertheless, 14 cases of peripheral neuropathy occurring during leflunomide treatment for rheumatoid arthritis have been reported to the regional pharmacovigilance centre in Bordeaux (table 1).

The cases include seven men and seven women. Mean age at the start of treatment with leflunomide was 69 years (range 57–78). Median duration of treatment at the onset of neuropathy was 7.5 months (range 3 weeks−29 months). Median duration of disease at treatment onset was 8.2 years (range 1–20). All patients had previously received a 100 mg loading dose of leflunomide for 3 days and were treated with a 20 mg daily dose. All patients presented with paraesthesia. A nerve conduction study demonstrated either motor or sensory axonal neuropathy in four cases and sensory axonal neuropathy in 10 cases.

All the patients were concomitantly receiving several drugs. Four patients were diabetic. In two cases, retinal angiography did not disclose any diabetic macroangiopathy. In two patients (Nos 5 and 10), aspecific vasculitis was diagnosed by neuromuscular biopsy when the neuropathy was explored. No biopsy was performed for the others patient. In three patients (Nos 1, 5, and 12) the pANCA were positive. None of these cases were treated concomitantly with other neurotoxic DMARDs. One patient (No 12) was concomitantly treated with infliximab. Two patients (Nos 6 and 10) concomitantly received a statin for a long period. Another patient (No 6) was treated concomitantly with almitrine, a known neurotoxic drug. Nevertheless, the neuropathy did not resolve after almitrine was discontinued but improved after leflunomide was stopped. The condition of patient No 12, whose neuropathy was related to previous use of thalidomide, worsened as soon as leflunomide was prescribed. In two patients (Nos 5 and 8) a previous diagnosis of neuropathy was present. Nevertheless, the peripheral nervous system event also worsened as soon as the DMARD was started, with a much shorter delay of onset than in the other cases. Other possible causes of neuropathy (metabolic or immune disorders, vitamin deficiency, neoplasia, viral and bacterial serology, etc) were ruled out in all cases. In half of the patients, the neuropathy improved after 3–6 months when leflunomide was discontinued (no nerve conduction study was performed). In the other patients, the neuropathy did not worsen.

Although paraesthesia is mentioned in the drug's summary of product characteristics, we report here the first (as far as we know) case series of adverse peripheral nerve effects during leflunomide treatment. Although these neuropathies may be multifactorial, the individual cases (delay of onset of the neuropathy and improvement after the DMARD was stopped) seem to suggest that this drug may be neurotoxic.

**Table 1** Characteristics of patients with suspected leflunomide associated peripheral neuropathy

| Characteristic | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age at onset | 64 | 66 | 72 | 77 | 80 | 70 | 61 | 78 | 59 | 69 | 64 | 75 | 75 | 59 |
| Sex | M | F | F | M | M | M | F | F | F | M | M | M | F | F |
| Duration of disease (years) | 5 | 17 | 1 | 6 | 1 | 10 | 15 | 3 | 5 | 20 | 11 | 3.3 | 9 | 43 |
| Duration of treatment at onset of neuropathy (months) | 10 | 19,1 | 1.7 | 19 | 3.2 | 1 | 12 | 0.6 | 29 | 2 | 5 | 2 | 24 | 17 |
| Neurological status before leflunomide | Normal | Normal | Normal | Normal | Dysaesthesia | Normal | Normal | Hypoaesthesia | Normal | Normal | Normal | Dysaesthesia | Normal | Normal |
| Diabetes mellitus | No | No | Yes | Yes | Yes | No | Yes | No | No | No | No | No | No | No |
| No previous or concomitant neurotoxic drug | – | – | – | – | – | Almitrine | – | – | – | Atorvastatine | – | Thalidomide | – | – |
| CNS | SAN | MSAN | SAN | MSAN | MSAN | SAN | SAN | MSAN | SAN | SAN | SAN | SAN | SAN | SAN |
| pANCA | Yes | No | No | No | Yes | No | No | No | Un | Un | No | Yes | No | No |
| Concomitant drugs | 1, 3, 4, 8 | 1, 2, 3, 5, 8 | 5, 6 | 1, 3, 4, 7 | 1, 4, 5 | 1, 2, 4, 5 | 1, 2, 3, 8, 9 | 1, 2 | 1, 2, 4, 5 | 1, 4 | 1, 2, 4, 6 | 1, 3, 4, 5, 8 | 2, 3, 4 | 2, 3, 4 |
| Washout* | Yes | No | No | No | No | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes |
| Outcome after stopping drug | Stabilisation | Recovery | Improvement | Stabilisation | Stabilisation | Improvement | Improvement | Stabilisation | Improvement | Stabilisation | Stabilisation | Improvement | Continuing | Improvement |

M, male; F, female; MSAN, motor and sensory axonal neuropathy; SAN, sensory axonal neuropathy; *washout, 10 days cholestyramine after stopping leflunomide; Un, unknown; major concomitant drug: 1, corticosteroids; 2, non-steroidal anti-inflammatory drugs; 3, analgesics; 4, antiulcer drugs; 5, antihypertensive drugs; 6, antidiabetic drugs; 7, anticoagulant drugs; 8, vitamin D substances.

A report of only one other case has been published previously.[8] To date, five other cases have been reported to the French pharmacovigilance system[9] over a period of 2 years.

Carulli and Davies suggested that the neuropathy might be due to a neurological vasculitis induced by leflunomide.[8] In the absence of a neuromuscular biopsy, this hypothesis could not be confirmed, but it is supported by a case report of cutaneous vasculitis induced by leflunomide without any neurological disorder.[10] Moreover, two cases in this case series presented with aspecific vasculitis diagnosed by neuromuscular biopsy when the aetiology of the neuropathy was explored.

Clearly, clinicians should be aware of the possibility of peripheral neuropathy in patients treated with leflunomide, especially when other risk factors are present. This does not detract from the usefulness of this drug in the treatment of rheumatoid arthritis.

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# Tumour necrosis factor α antagonists and early postoperative complications in patients with inflammatory joint disease undergoing elective orthopaedic surgery

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Tumour necrosis factor α (TNFα) antagonists are now established as therapeutic agents for active rheumatoid arthritis (RA) resistant to conventional drug treatment.[1] However, they decrease resistance to infection, including unusual infections such as tuberculosis,[2 3] and in an experimental setting have been shown to impair wound healing.[4] Previous studies have shown that TNFα antagonists do not increase the risk of postoperative surgical complications in patients with Crohn's disease who undergo resective bowel surgery,[5 6] but the safety of these drugs in patients with RA who undergo elective orthopaedic surgery has not yet been established.

As over 10% of patients with RA at our institution receiving antirheumatic drugs still require some form of elective orthopaedic surgical intervention we carried out a retrospective study of patients who received anti-TNF drug treatment before elective orthopaedic surgery.

Depending on the complexity, operations were divided into major surgery, including joint replacement surgery and lower limb arthrodeses; minor cases, including day case surgery;

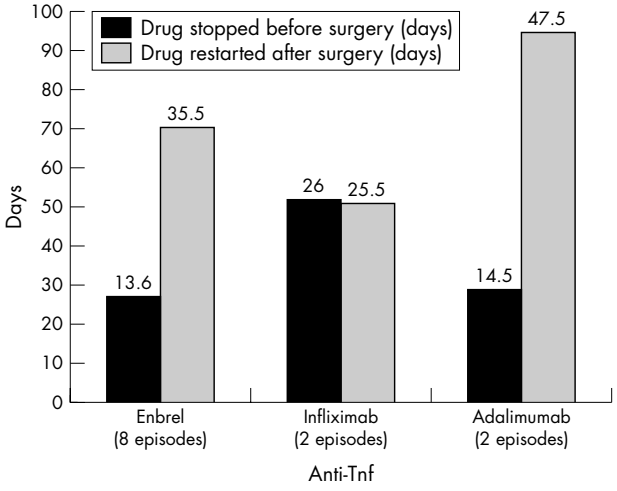


**Figure 1** Time at which drug treatment was stopped and restarted.