An “n of 1” trial of intravenous immunoglobulin treatment for chronic inflammatory demyelinating polyneuropathy

One small double blind study has found intravenous immunoglobulin (IVIG) to be effective in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). We describe an “n of 1” trial in a patient who received IVIG and who considered that “it worked.”

In 1968, when 37 years old, the man developed transient upper limb paraesthesiae. In 1970, these symptoms returned in both hands and feet together with muscle soreness and difficulty with balance. Examination showed weakness of ankle dorsiflexion, slight intention tremor of the upper limbs, areflexia, and glove and stocking sensory loss. The CSF protein was 1.9 g/l, 30% of which was γ globulin. No cells were present. Peripheral nerve conduction velocities were reduced. The next year he developed sensory loss below the knees. Treatment with prednisolone was started and the response was striking. In 1978, aza- thioprine was added. His subsequent course was characterised by relapses and remissions with poor muscle power and mild brownish discoloration of the face. In 1985, an intravenous infusion of IVIG (0.4 g/kg/day) was given for five days. Limb function improved considerably so that he no longer used a walking stick. The same dose was repeated every three weeks until November and then withheld for the next six months during which the patient’s walking deteriorated. Subsequent treatment with IVIG (0.4 g/kg/month) again seemed successful, prompting a formal evaluation in September 1990.

A double blind placebo controlled single patient study was divided into four sequences of treatment, each consisting of four infusions, two placebo and two active (figure). Each infusion was given once every three weeks over 48 (4 × 4 × 3) weeks. The placebo was albumin and the study preparation was IVIG (0.4 g/kg) given over about two hours. Before the study started and immediately before each infusion, a standardised neurological assessment was made. The outcomes were (a) time to walk 10 metres, (b) maximum number of squats in 30 seconds, (c) maximum range of ankle dorsiflexion, and (d) the patient’s opinion as to whether he had received IVIG or placebo. The patient declined repeated nerve conduction studies. He continued to take prednisolone (20 mg) on alternate days and azathioprine (50 mg per day).

There was no definite treatment effect objectively. The probability that the patient would correctly identify the treatment on 11 or more of the 14 occasions, however, was significant (p = 0.03 (one sided test)). The lack of a major treatment effect could reflect the lack of a simple, reliable, valid, and communicable measure of outcome. The time to walk 10 metres and the number of squats in 30 seconds, although objective, are insensitive and have a definite “ceiling” effect, particularly as the patient had only mild proximal weakness. Perhaps we should have timed his walking over a longer distance. The range of ankle dorsiflexion is subject to considerable within and between observer variation. Possibly the best indicator was the patient’s own opinion (he was correct on all but three occasions) but it could be argued that this was not a patient blind assessment because some patients describe a “kick” soon after receiving IVIG.

Whether the lack of effect in this patient reflected the concurrent use of immunosuppressives; the severity of his “burnt out” disease with little capacity for recovery; the possibility that he may have responded to IVIG at one time, but not at another, becoming more refractory to any form of treatment as the disease advanced; the fact that he was a real “non-responder”; or we were mistaken and the patient was correct, remains unknown. Nevertheless, this study illustrates some of the difficulties that will be encountered in any randomised controlled trial, notwithstanding the considerable expense of the treatment and the time and effort it took to perform even an “n of 1” trial.

If a large trial were to be undertaken, a prespecified hypothesis should be that subgroups of patients with CIDP exist (some may respond to IVIG and others not). More importantly, better measures of outcome are necessary; patients may have different types of disability, and the accurate assessment of each demands more thought than we anticipated. Although our neuropsychological studies are objective they may not reflect function and may not be tolerated. Perhaps the Rankin scale is the most appropriate simple and reliable measure of functional outcome, despite being relatively subjective. After all, if a treatment as costly as IVIG is going to be used, it should improve function by a degree that could be detected on the Rankin scale.

Peripheral neuropathy associated with dialysis amyloidosis

Haemodialysis associated amyloidosis (also called β2 microglobulin amyloidosis), a novel type of secondary amyloidosis, is a frequent complication in patients with chronic renal failure on prolonged maintenance haemodialysis, lasting seven or eight years. The usual manifestations are rheumatological. We describe a motor and sensory neuropathy associated with dialysis amyloidosis.

A 55 year old woman developed renal failure due to biopsy proved crescentic glomerulonephritis and had been on maintenance haemodialysis with cuprophane membranes for 10 years. After eight years on dialysis she developed weakness and numbness and dysaesthesia in the lower extremities. In August 1992, she was admitted to our hospital for evaluation of these symptoms. Her medical history and family history were unremarkable. Cranial nerves and autonomic function were normal. There was distal weakness and wasting of the lower but not of the upper limbs. Sensory examination showed distal and symmetric hypoesthesia in the lower limbs, involving all modalities of sensation. Tendon reflexes were normal at the knees and absent at the ankles. There were no pathological reflexes, no signs of carpal tunnel syndrome, and no signs of systemic amyloidosis.

Routine blood tests were normal. Serum β2 microglobulin concentration was 86-4 mg/l (Pharmacia radioimmunoassay; normal <3 mg/l). There was no Bence-Jones proteinuria or a monoclonal immunoglobulin on serum protein electrophoresis. Moderate amounts of long duration polyphasic high amplitude motor units were found by EMG in the muscles of the lower limbs. The motor nerve conduction velocity