High-dose intravenous human immunoglobulin in polymyositis resistant to treatment

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Abstract
Two patients were treated with treatment-resistant polymyositis with intravenous immunoglobulin over four days at a dose of 0.4 g/kg/day. Clinical recovery followed within two months. Serum creatine kinase (CK) activity decreased to normal, and a clear improvement in muscle strength was observed. One patient showed neither clinical relapses nor increase in serum CK activity after 20 months. The other showed a mild increase in serum CK activity after 24 months and was successfully retreated with intravenous immunoglobulin. There were no significant adverse side effects.

Polymyositis is a chronic inflammatory disorder of striated muscle and is characterised by muscle weakness. The aetiology remains unknown, but advances in technology suggest that immunological mechanisms contribute to muscle and connective tissue injury. Corticosteroids alone or in association with immunosuppressive drugs such as azathioprine, methotrexate, cyclosporine, or cyclophosphamide are the primary pharmacological treatment, but a high percentage (31–36%) of patients do not benefit from this therapy. Because of this and the morbidity associated with use of corticosteroids, additional therapeutic measures, such as lympho-plasmapheresis and total body irradiation, have been sought for the management of the disease.

High dose intravenous human immunoglobulin has been reported to produce improvement in some neurological diseases such as CIDP, MG, and demyelinating neuropathy associated with monoclonal gammopathy. So far intravenous immunoglobulin has been administered only in one case of treatment-resistant chronic polymyositis, with only partial improvement in muscle strength and in muscle enzyme elevation. We describe rapid improvement in muscle strength and ancillary examination in two cases of treatment-resistant chronic polymyositis after iv administration of immunoglobulin. These are the only two cases in which we have tried intravenous immunoglobulin.

Subjects and methods
The diagnosis of polymyositis was supported by clinical examination, laboratory findings, needle EMG, and muscle biopsy specimens. The grading system used for disability was the one used by Rose and Walton: 1—no abnormality on examination and full functional recovery; 2—no abnormality on examination but easily tired with reduced exercise tolerance; 3—minimal degree of atrophy or weakness in one or more muscle groups without functional impairment; 4—incomplete recovery, waddling gait, unable to run, but able to climb stairs without needing arm support; 5—incomplete recovery, noticeble waddling gait, and accentuated lumbar lordosis, unable to climb stairs or raise from a standard high chair without needing arm support; 6—unable to walk without assistance. Intravenous immunoglobulin (Gammavenin, Ist. Behring, Italy) was given over four days at a dose of 0.4 g/kg/day. Patients were followed up for several months by clinical or laboratory examinations or both, each month.

Patient I
A 55 year old woman developed severe muscle pain and weakness in the upper and lower limbs in June 1980. She was unable to climb stairs or put objects on a high shelf. She was admitted to our clinic in July 1980. Neurological examination showed weakness in the muscles of the shoulder, pelvic girdle, and neck. All deep tendon reflexes were absent. Sensory perception was normal. Laboratory findings showed decreased serum creatine kinase (CK) activity (6200 IU/l; normal <170 IU/l), LDH (800 IU/l; normal 250–450), SGOT (210 IU/l; normal <40), SGPT (140 IU/l; normal <40), ESR (95 mm in the first hour) and serum levels of alpha 2 globulins (11.2%; normal 4.7–8.3%). All other laboratory tests were normal. Needle EMG showed a myopathic pattern with abnormally brief action potentials of low amplitude and fibrillation potentials in the muscles of shoulder and pelvic girdle. Muscle biopsy specimens of the left brachial biceps showed many degenerating fibres and inflammatory infiltrates. Steroid treatment (prednisone 50 mg daily over a month then reduced to 50 mg on alternate days until June 1981) only slightly
improved muscle strength and laboratory results (CK 1859 IU/l). In February 1982 a new course of steroids (prednisone 50 mg daily over two months) was followed by only short term clinical improvement and decrease in serum CK. In April 1982 she developed dysphagia and became unable to walk. In July 1982 she was treated with prednisone 75 mg every day until September and then with 75 mg on alternate days until December when she noted an improvement in muscle strength: she could walk unaided but often fell. Serum CK was 461 IU/l. General examination showed serious side effects of weight gain, cushingoid appearance, and bilateral cataract. Steroid treatment was discontinued and immunosuppressive treatment with azathioprine 150 mg daily was started. In July 1983 her serum CK was 1540 IU/l; she was unable to walk unaided or keep her arms outstretched. In November 1983 her serum CK was 5600 IU/l. She underwent plasma exchange (five courses) without clinical improvement. Steroid treatment was re-started with prednisone 50 mg on alternate days until July 1984 and then discontinued. As steroid treatment was followed by a reduction in CK activity (681 IU/l at the end of the treatment) and a mild improvement in muscle strength, the patient underwent several courses. In March 1986 general examination revealed cushingoid appearance, weight gain (23 kg), bilateral cataract, osteoporosis, and mild diabetes mellitus. She underwent total body irradiation (150 Rad in ten times) but neither clinical nor laboratory results (CK 1200 IU/l) were notable.

In October 1987 her serum CK was 1000 IU/l, and she was unable to walk unaided. She was treated with intravenous immunoglobulin 0.4 g/kg/daily over five days and steroid treatment was discontinued. One month later her serum CK was 400 IU/l, and she could walk unaided. In December 1987, CK activity was normal, and neurological examination showed only mild proximal limb weakness. The patient was followed up for 20 months and experienced no clinical relapses or increase in CK activity until July 1989, when laboratory results showed mild increase (200 IU/l). No muscular weakness was present at neurological examination. Steroid therapy was re-started at a low dosage (25 mg daily). In December 1989 she began to complain of muscle weakness. In February 1990 CK activity was 567 IU/l and ESR was 110 mm. Steroid treatment was discontinued, and she was retreated with intravenous immunoglobulin. In April 1990 CK activity had decreased to 204 IU/l, and there was a remarkable improvement in muscle strength.

Patient 2
A 57 year old woman noted the onset of pain and proximal weakness in the upper and lower limbs in July 1985. She had increasing difficulty in going up stairs and combing her hair. In September 1985 she became unable to walk and developed dysphagia and dysphonia and was admitted to our clinic. Neurological examination showed severe proximal weakness of limb, trunk, and neck muscles. Pharyngeal and laryngeal muscles were also affected. All deep tendon reflexes were absent. Sensation was intact. Her serum creatine kinase (CK) activity was 5847 IU/l (normal <170 IU/l), LDH was 1500 IU/l (normal: 250-450), SGOT was 222 IU/l (normal <40), SGPT was 186 IU/l (normal <40), ESR was 100 mm (first hour), and alpha 2 globulins were also abnormally high (16-3%; normal 4.7-8.3%). Other laboratory tests were normal including an ECG and thoracic, upper, and lower abdominal total body scan. Needle EMG revealed fibrillation potentials and many brief action potentials of low amplitude in all muscles. Muscle biopsy specimens of the left biceps brachii showed clear fibre size variability, many degenerating fibres, and diffuse perivascular inflammatory response. Steroid treatment, started at a daily dose of 75 mg prednisone over a month, and then reduced to 50 mg daily, caused only slight improvement in muscle strength and produced no effects on the increased serum enzyme activity (CK 4540 IU/l). In January 1986 she was still unable to walk and could stand only if aided. CK activity was 3840 IU/l. General examination showed weight gain and cushingoid appearance. She developed behaviour disturbances that were successfully treated with haloperidol. Steroid treatment was reduced to 25 mg prednisone daily and azathioprine 100 mg daily. She was then admitted to a department for a long term rehabilitation and physiotherapy. In April 1986 steroid treatment was reduced to 25 mg prednisone on alternate days and azathioprine was discontinued because she developed leukopenia.

In July 1987 she was able to stand and walk a few steps with help. Dysphagia and dysphonia were still present; CK activity was 2500 IU/l. She was treated with intravenous immunoglobulin at a dose of 0.4 g/kg/daily for five days, and steroid treatment was discontinued. In August 1987 CK activity was 1318 IU/l, and she noted an improvement in muscle strength. In September 1987 she was able to stand and walk without help. Dysphagia and dysphonia were no longer present. CK activity was 618 IU/l. In October 1987 she was able to climb stairs, and CK activity was normal (80 IU/l). Neurological examination showed only a mild proximal weakness in the lower limbs. She was followed up until October 1989 and showed neither clinical relapses nor increase in CK activity.

Discussion
Although this was an uncontrolled study, our patients’ improvement was temporally related to the administration of immunoglobulin. Moreover, both patients had previously been treated unsuccessfully with steroids and immunosuppressive drugs. No spontaneous remission was seen in either case before intake of intravenous immunoglobulin. Administration was (eight years and two years). Benefits were sustained in one case and temporary in the other, in whom further intravenous immuno-
globulin was administered, which was followed by clinical and laboratory improvements. Why intravenous immunoglobulin is beneficial to patients with polymyositis is unknown. A positive clinical effect could be ascribed to an increased T cell suppressor function or nonspecific effects on natural killer cells.18-21 Other diseases, long term remission has been related to saturation of Fc receptors on macrophages21 or solubilisation of immune complexes by intravenous immunoglobulin in a complement-independent reaction.22

No adverse effects were seen during intravenous immunoglobulin administration. The gammaventin which we used is screened for HIV and hepatitis B antigens and has not been associated with transmission of hepatitis C. The main drawback of intravenous immunoglobulin treatment is its high cost.

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