Pulsed high-dose dexamethasone treatment of polyneuropathy associated with monoclonal gammaopathy (letter)

Notermans, N.C.; Vermeulen, M.; Lokhorst, H.M.; van Doorn, P.A.; Berg, L.H.; Teunissen, L.L.; Wokke, J.H.J.

DOI
10.1007/s004150050124

Publication date
1997

Published in
Journal of neurology

N. C. Notermans
M. Vermeulen
H. M. Lokhorst
P. A. Van Doorn
L. H. Van den Berg
L. L. Teunissen
J. H. J. Wokke

Pulsed high-dose dexamethasone treatment of polyneuropathy associated with monoclonal gammopathy

Received: 24 January 1997
Received in revised form: 13 April 1997
Accepted: 28 April 1997

Sirs: Polyneuropathy associated with monoclonal gammopathy of undetermined significance (MGUS) is an incapacitating disorder that often runs a progressive course [7]. Evidence that MGUS autoantibody activity causes peripheral neuropathy has provided a rational basis for therapeutic intervention directed at lowering the monoclonal (M) protein concentration [4]. The optimal treatment regimen in terms of benefit and side effects is unknown. Although chemotherapy, with or without plasmapheresis, seems to be effective in some patients, it has potentially serious side effects [3, 6, 8, 9]. Treatment with pulsed high-dose dexamethasone is usually well tolerated [1, 2]. Based on the efficacy of dexamethasone as monotherapy in patients with multiple myeloma [1] and therapeutic resistant idiopathic thrombocytopenic purpura [2], we treated patients with a progressive polyneuropathy associated with MGUS with pulsed high-dose dexamethasone (40 mg per day orally for 4 consecutive days once a month in 6 cycles).

From 1993–1995, six patients with a progressive polyneuropathy associated with MGUS were treated with dexamethasone. None of the patients had previously been treated with immunosuppressive or cyctostatic therapy. The mean follow-up was 19 months (SD 5 months). Five patients had IgM-MGUS, all with anti-myelin associated glycoprotein (MAG) antibodies, and one had only IgG-MGUS. Bone marrow biopsy showed no more than 10% plasma cells or more than 30% lymphoid cells, and no amyloid deposition (Congo red staining). Malignant plasma cell dyscrasias were excluded and no other cause of neuropathy was found.

The mean age at onset of the neuropathy was 59 years (SD 8). In all patients the sensory features of the neuropathy were more pronounced than the motor abnormalities. Electrophysiological studies showed a demyelinating neuropathy in two patients, axonal degeneration in one (IgG patient) and both demyelinating and axonal in three patients. Sural nerve biopsies were performed in four patients. Two patients had findings consistent with demyelination and two with demyelination and axonal degeneration. In three patients deposition of IgM was demonstrated. Mononuclear cell infiltrates were not present and Congo red staining was negative.

Treatment with dexamethasone was started because of progression of the neuropathy. After treatment two patients showed improved symptoms and signs (improvement = improvement of 1 or more points on the Rankin scale), with the onset of improvement 3 and 6 months after beginning treatment respectively (Table 1). The changes noted were a reduction in numbness, paraesthesia and improvement in strength [motor sumscore – summation of test results of six muscles of each arm and six

Table 1 Clinical and laboratory findings before and after treatment with dexamethasone (*MGUS* monoclonal gammopathy of undetermined significance, *b* before treatment, *a* after treatment, *no* not obtainable, *nd* not done, *ax* axonal degeneration, *dem* demyelination, *mix* axonal degeneration and demyelination

Patient	Age (years)	MGUS	Level MGUS (g/l)		Motor sumscore[a]		Disability scale		ΣCMAP[b] (mV)		ΣSNAP[c] (muV)		Ax/Dem/ Mix	Side effects
			b	a	b	a	b	a	b	a	b	a		
1	70	IgMκ	5	3	105	110	3	2	12.7	15.6	no	no	dem	Mood disturbances, paraesthesia, weakness in proximal lower limbs
2	47	IgMκ	< 1	< 1	112	116	3	2	8.8	9.3	no	7.9	dem	None
3	56	IgMκ	< 1	< 1	110	110	2	2	14.9	nd	4.0	nd	mix	None
4	65	IgMκ	5	4	110	110	2	2	6.5	6.8	2.1	2.0	mix	Pain arm/leg, mood disturbances, paraesthesia
5	69	IgGκ	< 1	< 1	114	116	2	2	13.1	nd	20.1	nd	mix	Weakness in proximal lower limbs
6	65	IgMλ	5	4	116	108	3	4	4.6	3.8	no	no	dem	Mood/sleep disturbances, weakness in proximal lower limbs

[a] *Motor sumscore* summation of test results of 6 muscles of each arm and 6 muscles of each leg using the MRC grading system (maximum score 120)
[b] *ΣCMAP* summation of the compound muscle action potentials of median and peroneal nerve
[c] *ΣSNAP* summation of the sensory nerve action potentials of median and sural nerve

muscles of each leg using the MRC grading system (maximum score 120)]. Follow-up of these two patients has now been longer than 20 months. In three patients the neuropathy stabilized for more than 12 months of follow-up (stabilization = no change on the Rankin scale). Patient 6 further deteriorated and became wheelchair-bound despite treatment with dexamethasone (deterioration = deterioration of 1 or more points on the Rankin scale). After a period of 3 months without therapy, he received cyclophosphamide 500 mg for 4 days combined with prednisone 60 mg for 5 days at 4-week intervals for 6 months. After 6 months of cyclophosphamide therapy, the ataxia diminished and strength increased, so that he could walk again. The M-protein decreased to 2 g/l.

Four patients had serious side effects using WHO criteria (Table 1) [2]. Three patients suffered from severe mood disturbances during dexamethasone treatment and experienced the therapy as a rough remedy, greatly influencing their daily lives. One patient (4) wanted to stop after four cycles owing to these side effects and refused further treatment. Because of the observed side effects, enrolment was stopped after 6 patients.

We studied whether pulsed high-dose dexamethasone treatment was effective in patients with a progressive polyneuropathy associated with MGUS, as we anticipated a potential immunosuppressive effect, by elimination of malignant plasma cells and/or reduction of aberrant immunoglobulin production [1, 2]. In contrast to the mild side effects reported in the literature on pulsed high-dose dexamethasone treatment, we encountered a very high frequency of serious invalidating side effects [1, 2]. This is in contrast with high-dose dexamethasone treatment in patients with chronic inflammatory demyelinating polyneuropathy. Of ten patients, only one had serious side effects [5]. In this group of ten patients six had a clear beneficial response to treatment [5]. Possibly patients with polyneuropathy associated with MGUS are more susceptible to the toxic effects of high-dose dexamethasone. Therefore, although treatment with pulsed high-dose dexamethasone may prevent worsening of the neuropathy, we cannot recommend pulsed high-dose dexamethasone treatment as the first choice for patients with polyneuropathy associated with MGUS.

References

1. Alexaminn R, Dimopoulos MA, Delassalle K, Barlogie B (1992) Primary dexamethasone treatment of multiple myeloma. Blood 80: 887–890
2. Andersen JC (1994) Response of resistant idiopathic thrombocytopenic purpura to pulsed high-dose dexamethasone therapy. N Engl J Med 330: 1560–1564
3. Dyck PJ, Low PA, Windebank AJ, Jaradeh SS et al. (1991) Plasma exchange in polyneuropathy associated with monoclonal gammopathy of undetermined significance. N Engl J Med 325: 1482–1486
4. Latov N (1995) Pathogenesis and therapy of neuropathies associated with monoclonal gammopathies. Ann Neurol 37 (S1): S32–S42
5. Molenaar DSM, Van Doorn PA, Vermeulen M (1997) Pulsed high-dose dexamethasone in chronic inflammatory demyelinating polyneuropathy: a pilot study. J Neurol Neurosurg Psychiatry 62:388–390
6. Nobile-Orazio E, Baldini L, Barbieri S, Marmiroli P, et al. (1988) Treatment of patients with neuropathy and anti-MAG IgM M-proteins. Ann Neurol 24: 83–97
7. Notermans NC, Wokke JHJ, Lokhorst HM, Franssen H, et al. (1994) Polyneuropathy associated with monoclonal gammopathy of undetermined significance. A prospective study of the prognostic value of clinical and laboratory abnormalities. Brain 117: 1385–1393
8. Notermans NC, Lokhorst HM, Franssen H, Van der Graaf Y, et al. (1996) Intermittent cylcophosphamide and prednisone treatment of polyneuropathy associated with monoclonal gammopathy of undetermined significance. Neurology 47: 1227–1233
9. Oksenhendler E, Chrevet S, Léger J-M, Louboutin J-P et al. (1995) Plasma exchange and chlorambucil in polyneuropathy associated with monoclonal IgM gammopathy. J Neurol Neurosurg Psychiatry 59: 243–247

N. C. Notermans · L. H. Van den Berg
L. L. Teunissen · J. H. J. Wokke
The Rudolph Magnus Institute
of Neurosciences,
Department of Neurology,
University Hospital Utrecht,
The Netherlands

M. Vermeulen
Department of Neurology,
Academic Medical Centre Amsterdam,
The Netherlands

P. A. Van Doorn
Department of Neurology,
University Hospital Rotterdam,
The Netherlands

H. M. Lokhorst
Department of Hematology,
University Hospital Utrecht,
The Netherlands

N. C. Notermans (✉)
Department of Neuromuscular Disorders,
University Hospital Utrecht,
C03.236, PO Box 85500,
3508 GA Utrecht, The Netherlands
Tel.: 31-30-506564,
Fax: 31-31-542100