Treatment of inclusion body myositis with cyclosporin-A or tacrolimus: successful long-term management in patients with earlier active disease and concomitant autoimmune features

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Abstract

Objectives

Sporadic inclusion body myositis (s-IBM) is a chronic, progressive, inflammatory myopathy of unknown aetiology, generally resistant to immunosuppressive therapy. Given that lymphocyte infiltrates in s-IBM muscle tissue are CD8+ T cells, targeting these cells may represent a valid approach.

Patients and methods

Three patients with biopsy-proven s-IBM, high creatine kinase levels at diagnosis, two of whom with associated immune disorders, were treated with either cyclosporin-A (CyA) or tacrolimus, in combination with high doses of corticosteroids (CS), followed by rapid CS tapering. Clinical assessment and laboratory evaluation were performed every three months for the first year and then every six months for the second year.

Results

Based on muscle strength assessment and muscle enzyme serum levels, a major clinical response was observed at month +3 in two out of the three patients. A complete clinical response and major clinical response were obtained at month +6, in two and one patient, respectively. Normalization of serum muscle enzymes was observed in all. Steroids could be tapered to very low doses in all patients and were suspended early in one. Laboratory, but not clinical relapse occurred in one patient and was controlled by increasing the CyA dose. Treatment was well tolerated, with no serious adverse events occurring. All three patients are maintaining immunosuppressive therapy.

Conclusions

Calcineurin inhibitors may represent a useful option for the long-term management of s-IBM, possibly in a subset characterized by a short duration with high disease activity or associated autoimmune manifestations.

Key words
Inclusion body myositis, cyclosporin-A, tacrolimus, T cell.

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Introduction

Sporadic inclusion body myositis (s-IBM) is the most common inflammatory myopathy in patients over 50; it is characterized by slowly progressive muscle weakness, usually delayed diagnosis and treatment is often unsatisfactory (1, 2).

Diagnostic criteria for s-IBM are both clinical and morphological (3) and identify a definite and a probable category of disease, the main differential diagnosis being polymyositis (4). Definite diagnosis depends on pathologic findings on muscle biopsy: lymphohystiocytic infiltrate at least focally penetrating non-necrotic muscle cells in endomysial position; rimmed vacuoles; intracellular amyloid deposits or 15-18 nm tubofilamentous inclusions on electron microscopy associated with intracytoplasmic, non-membrane bound, membranous whorls (3, 4). Morphology in s-IBM varies in relation to time from onset of disease to biopsy (3), and, in particular, rimmed vacuoles may not be seen in early stages.

Corticosteroids or other immunosuppressive therapies generally fail in s-IBM (5), although steroids may sometimes give a short-term benefit (2). The efficacy of intravenous immunoglobulins is still unclear (6, 7). On the other hand, a subgroup of patients with s-IBM and associated autoimmune disorders, present in about 15% of cases (8), appears to benefit from immunosuppressive treatment (9, 10).

Based on novel data regarding local characteristics of the inflammatory infiltrating clonal T cells (11), calcineurin inhibitors, which interfere with T cell activation and proliferation, were administrated in conjunction with corticosteroids to three consecutive patients with biopsy proven s-IBM.

Patients and methods

Three consecutive, unselected patients with s-IBM, all females, were treated with calcineurin inhibitors and high-dose steroids, the latter being rapidly tapered. The characteristics of the patients, clinical presentation, results of electromyography and the salient features of morphological evaluation are shown in Table I.

Rheumatoid factor, antinuclear and antiphospholipid antibodies were tested.

Routine blood tests, including serum creatine kinase (sCK), lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, aldolase and myoglobin, were evaluated at baseline and at each time point in follow-up (month +3, +6, +9, +12, +18 and +24).

Muscle strength was evaluated in all muscle groups at the same time point and graded, according to the Medical Research Council of Great Britain, from 0 (complete paralysis) to 5 (normal strength) (12). The response to therapy was defined as follows: i) complete response: improvement to grade 5, starting from any grade below 5 at baseline; ii) major response: improvement to grade 4, starting from any grade below 4 at baseline; iii) minor response: any improvement not reaching grade 4 or 5. No response was defined as no improvement or worsening; relapse or progression when decrease of at least one grade in muscle strength occurred after treatment (12). The score recorded for evaluation of clinical response at each time point was the lowest found in the muscle groups.

Case histories

Case 1

A 47-year-old woman with a history of chronic autoimmune thyroiditis of 12 years duration, who developed weakness of the proximal muscles of the lower limbs associated with muscle soreness 9 months previously, was admitted in March 2002 for a worsening of the weakness in proximal lower limb muscles and recent involvement of the shoulder and pelvic girdle muscles. High muscle enzyme levels were observed. Physical examination revealed bilateral weakness of the shoulder girdle (supraspinate, infraspinate and deltoid), mild involvement of right and left hamstrings and of the pelvic girdle muscles (gluteal and ileopsoas). Electromyography was consistent with an inflammatory myopathy. The findings on muscle biopsy are shown in detail in Table 1, confirming the diagnosis of s-IBM.

The patient was started on cyclosporin-A (CyA) 3 mg/kg/day with high-dose steroids (prednisone 1 mg/kg/day).

Table I. Clinical characteristics at diagnosis and features on muscle biopsy.

Patient N°.	1	2	3
Age, gender	49, F	62, F	73, F
Duration of symptoms (months)	9	24	39
Previous therapy for myopathy	none	none	IVIg, high-dose steroids, azathioprine, rituximab
Co-morbidities	chronic autoimmune thyroiditis (12 years duration)	none	chronic autoimmune thyroiditis (20 years duration); surgery for thymoma (3 years previously)[§]; arterial hypertension; type I diabetes
Site of muscle weakness at clinical presentation	proximal muscles of the lower limbs; bilateral involvement of the supra-spinate, infraspinate, deltoid gluteal and ileopsoas; mild involvement of right and left hamstrings	proximal upper and lower limb muscles; bilateral involvement of external shoulder rotators, hip abductors, diaphragm and intercostals	abductors, adductors and external rotators of the shoulder (bilateral), hip abductors and flexors (bilateral), neck extensors and paraspinals; mild involvement of right and left hamstrings
Anti-Jo-1	negative	negative	negative
Other auto-antibodies*	absent	absent	anti-acetylcholine receptor[#]
Electromyography	active myopathic process	active myopathic process	active myopathic process
Morphological diagnosis:	s-IBM	s-IBM	s-IBM
- % atrophic fibres	5	6	3
- % internalized nuclei	none	3	3
- endomisial non-necrotic fibres penetrated by lymphocytes	present	present	present
- rimmed vacuoles	absent	absent	absent
- non membrane bound, membranous whorls with associated tubo-filamentous inclusions	present	present	present
- immunohistochemical lymphocyte typing	CD3 +, CD20-	CD3 +, CD20-	CD3 +, CD20-

IVIg, intravenous immunoglobulins; s-IBM, sporadic inclusion body myositis.
[§]At 70, patient 3 had been subjected to thymectomy for thymoma, and nine months later developed clinical, laboratory and instrumental signs of an inflammatory myopathy. [#]A concomitant myasthenia gravis was excluded by clinical examination, repetitive nerve stimulation test and electromyography. *Rheumatoid factor, antinuclear antibodies, antiphospholipid antibodies.

Case 2

A 62-year-old woman with a history of slow and progressive muscle weakness of the lower and upper limbs of 24 months duration and recent development of weakness of the respiratory muscles was referred to our Clinic in May 2004. High muscle enzyme serum levels were found. Physical examination revealed bilateral weakness of the shoulder girdle (external shoulder rotators) and of the pelvic girdle muscles (hip abductors), of the diaphragm and intercostal muscles. Electromyography was consistent with an inflammatory myopathy. The findings on muscle biopsy are shown in detail in Table I, confirming the diagnosis of s-IBM. The patient was started on CyA 4 mg/kg/day with high-dose steroids (prednisone 1 mg/kg/day).

Case 3

A 73-year-old woman, with a history of adult onset type I diabetes, arterial hypertension and chronic autoimmune thyroiditis of 20 years duration, was admitted in July 2003 for severe muscle weakness of 39 months duration affecting the neck extensors, paraspinal, shoulder (abductors, adductors and external rotators), right and left hamstrings and pelvic girdle muscles (hip abductors and flexors). Three years previously she had been subjected to thymectomy for thymoma, and nine months later she developed clinical, laboratory and instrumental signs of an inflammatory myopathy. She was unsuccessfully treated with intravenous immunoglobulins and high dose steroids, with azathioprine and with rituximab in another Centre. High levels of muscle enzymes were evident at admission. Anti-acetylcholine receptor antibodies were detected, however, she lacked clinical evidence of myasthenia gravis and the results of repetitive nerve stimulation and electromyography all excluded this possibility. The findings on muscle biopsy are shown in detail in Table I, confirming the diagnosis of s-IBM. Figure 1 shows the ultrastructural features of the subplasmalemmal, non-

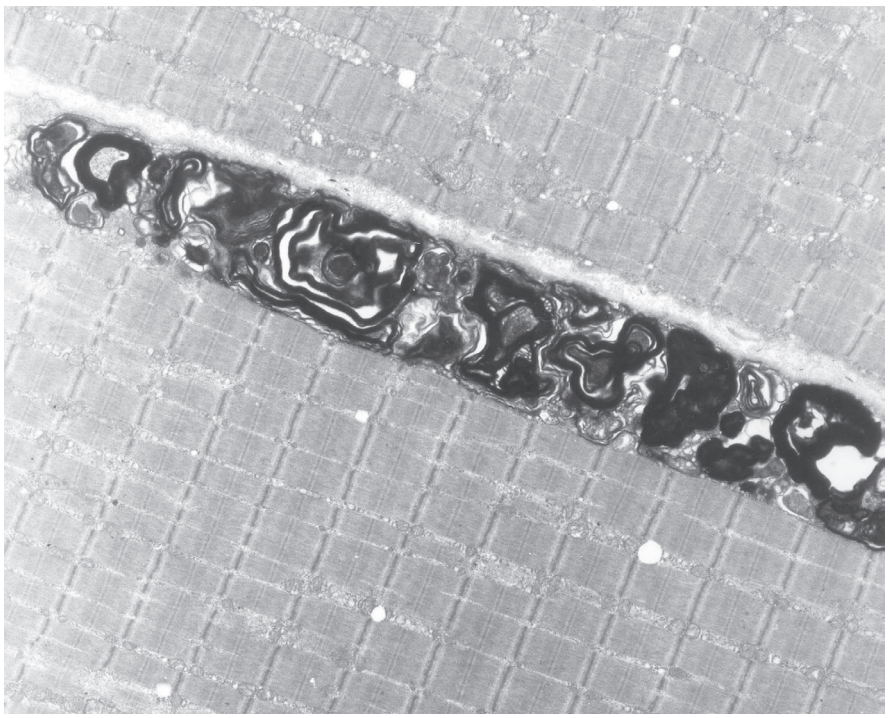

Fig. 1. Ultrastructural features of non-membrane bound inclusion bodies made of membranous whorls of various sizes and thickness in inclusion body myositis (original magnification 20.000x).

membrane bound, membranous whorls associated with tubofilamentous inclusions from this patient.

The patient was started on CyA 3 mg/kg/day with high-dose steroids (prednisone 1 mg/kg/day).

Treatment

Patient 1 maintained her regimen until month +18. An increase in sCK and myoglobin values was observed at month +12 and +18, without clinical relapse. Serum CyA concentration, evaluated at 8 a.m. pre-dose, was low (77 ng/ml) and CyA was increased to 4 mg/kg/day, with normalization of muscle enzymes and increase of CyA serum concentration to164 ng/ml. Prednisone was reduced to 0.3 mg/kg at the end of month +3. The patient was maintained on 5 mg/day of prednisone from month +6 to the last follow-up (month +24).

In patient 2 the CyA dose was increased to 5 mg/kg at the end of month +1 because of lack of clinical and laboratory

Table II. Laboratory findings and MRC score at baseline and during follow-up.

Patient N.°	sCK (mU/ml)	LDH (mU/ml)	Aldolase (mU/ml)	ALT (IU/L)	AST (IU/L)	Myoglobin (ng/ml)	MRC* score
Pt.1							
Baseline	4364	1445	36.9	116	99	648.3	3
+3	505	501	11	45	25	92.8	4
+6	165	424	2.7	28	14	33.3	5
+9	180	390	5.4	23	15	29.1	5
+12	621	415	6.6	30	22	51.1	5
+18	627	407	6.3	28	27	59.0	5
+24	163	277	5.2	23	28	25.4	5
Pt. 2							
Baseline	4941	1745	26.6	134	128	877.20	3
+3	583	724	15.5	60	42	573	4
+6	115	459	3.3	13	17	69.5	5
+9	125	183.5	ND	20	18	ND	5
+12	119	189	ND	20	20	ND	5
+18	105	209	ND	29	23	ND	5
+24	98	190.3	ND	15	24	ND	5
Pt. 3							
Baseline	1190	883	9.3	61	66	827	3
+3	255	412	5	40	34	54	3
+6	54	326	4.7	33	23	34	4
+9	78	351	5.1	25	21	37	4
+12	96	369	6	39	39	34	4
+18	51	315	4.5	25	20	35	4
+24	54	337	2.6	15	16	47	4

Pt: patient; MRC: Medical Research Council* (ref. 12); sCK: serum creatine kinase (normal range 25-190 mU/mL); LDH: lactate dehydrogenase (normal range 250-450 mU/mL); ALT: alanine aminotransferase (normal range 10-40 IU/L); AST: aspartate aminotransferase (normal range 10-40 IU/L); aldolase (normal range < 7,6 mU/mL); myoglobin (normal range < 100 ng/ml); ND: not done.

* Muscle strength will be recorded according to the Medical Research Council of Great Britain in six grades, from 0 (complete paralysis) to 5 (normal strength) (ref. 12).

response due to low serum CyA levels (137 ng/ml). CyA serum concentration then increased to 202 ng/ml at month +3 and to 238 ng/ml at month +6. Prednisone was reduced to 0.3 mg/kg at the end of month +3 and then tapered and suspended at month +7. The patient developed hypertension, well controlled with amlodipine.

In patient 3, CyA was soon interrupted because she developed a syndrome of inappropriate ADH secretion and severe respiratory failure. She was therefore maintained on high doses of steroids (prednisone 1 mg/kg/day) and CyA was substituted with tacrolimus 3 mg/day, reduced to 2 mg/day at month +3, when prednisone was rapidly tapered to 5 mg/day due to concomitant type I diabetes. She was maintained on 5 mg/day prednisone from month +3 to the last follow-up (month +24).

Clinical and laboratory response to treatment

A significant laboratory response was noticed in all three patients and a significant clinical response in patients 1 and 2 (Table II).

At month +3 a major clinical response in muscle strength and improvement in the laboratory parameters were seen in patients 1 and 2, while patient 3 showed a significant decrease of serum muscle enzymes, without a concomitant improvement in muscle strength.

At month +6, a complete clinical response and normalization of the laboratory parameters were evident in patients 1 and 2; in particular, the latter was able to carry out all her daily activities. Patient 3 demonstrated a slight improvement of muscle strength. From month +6 to the end of follow-up, all patients showed stable muscle strength scores. During treatment, no further muscle group showed a reduction in muscle strength scores.

Patients 1 and 2 showed an increase in laboratory parameters due to insufficient serum levels of CyA (month +12, patient 1; month +1, patient 2), duly corrected with normalization of muscle enzymes. No laboratory value relapse was observed when prednisone was reduced at month +3 in patients 1 and 2 or tapered in patient 3 to the maintenance dose.

The disease was stable in all the patients at the last follow-up at month +24.

Discussion

S-IBM is a progressive disease, with poor response to treatment (1-3), though immunosuppressive therapy may be effective in some cases (5-9, 13). Our results evidence a better response to immunosuppression in s-IBM cases, and highlight the role of calcineurin inhibitors as an effective and safe option in the long-term management in this setting, the rationale being that T cells, with a prevalence of CD8+ cytotoxic T lymphocytes, are the most prominent component of muscle inflammatory infiltrates (4, 11), hence this therapy was chosen to target T cells in this study.

All three patients were treated with calcineurin inhibitors in combination with steroids, which were rapidly tapered. This treatment appeared effective and safe after a follow-up of 24 months. There is only one published s-IBM case treated with CyA (14) and no data on tacrolimus therapy, while these drugs have been successfully used in some patients with polymyositis (15).

Our patients are not typical examples of s-IBM as far as sex, clinical presentation (only mild reduction in distal muscle force in 2/3) and high sCK levels at diagnosis are concerned (3). Two of them had a history of autoimmune thyroiditis. One underwent previous surgery for thymoma and showed positive anti-acetylcholine receptor antibodies, but no clinical evidence of myasthenia gravis. This type of presentation is unusual, but already described in the literature (3, 8, 10, 14, 16). It is possible that this subgroup of s-IBM patients may show a better response to therapy, possibly due to a different pathobiologic background linked to the autoimmune concomitant setting, as recently suggested (9, 13).

Even though not clinically typical, all had biopsy proven s-IBM, with pathological features allowing a definite diagnosis even though light microscopy did not disclose rimmed vacuoles. These are said to be difficult to find in early stage disease (3, 4), and, in fact, inclusion bodies were few and small; furthermore, rimmed vacuoles have been reported to be absent in a case associated with autoimmune disease (9). As further evidence of early stage disease, there was relatively limited tissue damage (few atrophic fibres, no fibrosis on histology). Furthermore, disease activity was high and, notably, the disease in these patients had been of short duration, ranging from 9 to 39 months, while usually, diagnosis is delayed for many years (2).

Overall, earlier diagnosis, higher sCK values and/or autoimmune features may be linked to s-IBM cases more prone to respond to immunosuppressors.

Given the clinically not typical features of these cases, ultrastructural examination was essential in defining them as s-IBM. The inclusion bodies described in s-IBM may be seen also in familiar cases (4), unassociated with inflammation; the latter being, on the other hand, clearly evident in our biopsy material. Furthermore, inclusion bodies are never seen either in hyper or in hypothyroidism, that may be associated with non-specific ultrastructural alterations to muscle fibres with no accompanying inflammation (4). Myasthenia gravis is characterized by either no abnormality or by type 2 fibre atrophy, focal inflammation and ultrastructural alterations to end plates; no membranous whorls or tubofilaments are seen (4).

Although it may be difficult to discriminate between the efficacy of either high-dose steroids or calcineurin inhibitors, or both, in inducing the clinical response observed in our cases, we noticed that relapse in patients 1 and 2 did not require re-induction with steroids, while a CyA dose increase was effective. Furthermore, the clinical response in the long term, with steroids rapidly tapered to very low doses or suspended, can be related to the therapeutic effect of calcineurin inhibitors.

In conclusion, T-cell targeting therapy with calcineurin inhibitors in combination with steroids was effective and safe in s-IBM, allowing steroid sparing in the long term. Even if s-IBM is generally considered resistant to treatment, a subset of s-IBM, i.e., cases of shorter duration, with concomitant autoimmune manifestations, and/or a higher degree of muscle inflammation, may

show a response. Calcineurin inhibitors should be further investigated in this subset of patients based on these favourable preliminary results, also in consideration of recent data supporting T-cell targeting in s-IBM (17).

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