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ORIGINAL COMMUNICATION

The long-term outcome of anti-Jo-1-positive inflammatory myopathies

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Abstract *Objective* To determine the response to treatment and the long-term outcome of patients with the antisynthetase syndrome associated with anti-Jo-1-antibodies. *Patients and Methods* A total of 12 patients with histologically proven myositis and anti-Jo-1-autoantibodies were evaluated over a mean follow-up period of 66.4 months. In all patients neuromuscular function tests, electromyographic examinations, pulmonary function tests and high-resolution-computed tomography of the lungs were performed regularly. *Results* Muscle function improved in all patients with treatment, and a complete clinical response was achieved in 5 patients. Pulmonary function worsened in 1 patient, who died from respiratory failure, but normalised in 4 patients. Arthropathy progressed despite improvement of myositis and pulmonary status in 2 patients. Discontinuation of treatment was facilitated in 1 patient, although long-term therapy was required in 10 patients. In 2 patients with refractory disease, treatment with intravenous immunoglobulins was successful. Severe side effects of treatment occurred in 7 patients and overall mortality rate was one of 12 (8 %). *Conclusion* The antisynthetase syndrome associated with anti-Jo-1-antibodies requires long-term immunosuppressive therapy in most patients. Whereas a complete clinical response of muscular symptoms is frequent, continued deterioration of the pulmonary system may occur despite immunosuppressive treatment, and may lead to fatal outcome. An interdisciplinary therapeutic approach is necessary for best possible results in these patients.

Key words Anti-Jo-1-antibodies · myositis · myopathy · interstitial lung disease

Introduction

Polymyositis and dermatomyositis form a heterogeneous group of inflammatory diseases primarily affecting skeletal muscle tissue. Cardinal symptoms are muscle weakness and increased creatine kinase (CK) activity. Among patients with inflammatory myopathies, a subgroup of patients sharing a number of clinical features has antibodies against various aminoacyl-tRNA synthetases. Clinical characteristics of the so-called antisynthetase syndromes are arthritis, Raynaud's phenomenon, mechanic's hands and interstitial lung disease [12, 14]. Patients are at risk of developing diffuse alveolitis, which may rapidly progress to respiratory failure [16]. The most common anti-synthetase antibody is the anti-Jo-1-antibody, which is found in about 20 % of patients with myositis [3, 21]. It is directed at the histidyl-tRNA synthetase. The overall prognosis of patients with anti-Jo-1-syndrome seems to be worse

than that of other inflammatory myopathies' subgroups.

We studied the long-term outcome of patients with anti-Jo-1-syndrome in a group of patients followed-up in our department.

Patients and methods

12 patients with myositis and anti-Jo-1-autoantibodies were followed-up during the past 14 years. Mean age at disease onset was 48.6 years (range 32–66). Male/female ratio was 1:2. The mean observation period was 66.4 months (range 46–127).

The diagnosis was made on the basis of clinical features of muscle weakness, and elevation of CK activity levels. All but one patient underwent open muscle biopsy. Specimens were examined by light and electron microscopy. Immunohistochemical analysis of the inflammatory cells was performed using antibodies against CD4, CD8, B-cells, and macrophages. Deposits of complement were detected by using antibodies against membrane attack complex (MAC).

Clinical assessment used the Angelini scores [1], and the "Functional grading scale" of Clarke [6], which records 11 daily living activities. Functions are graded from 0 (cannot do) to 3 (can do alone without difficulty).

A clinical relapse was defined as an increase of muscle symptoms, and as a sustained motor or pulmonary function decrease, or worsening of skin changes. A laboratory relapse was defined as a threefold increase of CK activity compared with the previous baseline level.

Electromyographic examinations with concentric needle electrodes were performed regularly in both proximal and distal muscles of the arms and legs. Spontaneous pathological activity (fibrillation potentials, positive sharp waves) was graded from 0 (absent) to +++ (present on any insertion).

Laboratory investigations included CK, CK-MB, SGOT, SGPT, C-reactive protein, and ANA-testing. Anti-Jo-1-antibodies were examined by immunodiffusion standard methods.

All patients underwent echocardiography.

Pulmonary function was assessed by a modified Medical Research Council (MRC) dyspnoea scale (1 = not troubled by breathlessness, 2 = respiratory distress when hurrying on the level or walking up hill, 3 = walks slower than most on ground level, 4 = stops because of respiratory distress after 100 yards walking distance, 5 = unable to leave home due to respiratory distress, 6 = oxygen treatment required 7 = mechanical ventilation required). In all patients pulmonary function tests, including spirometry, bodyplethysmography, carbon monoxide diffusion (TLCO) and blood gas measurements, were done regularly.

High resolution computed tomography was performed at 1 to 2 year intervals in all patients except patients 2 and 7. In all patients chest radiography was performed at intervals between 6 months and 2 years. An experienced radiologist evaluated the findings and their changes.

Results

Initial presentation

Onset of symptoms was subacute in 9/12 patients, and very slowly progressive (2 years) in 1 patient with a long period of increased fatiguability and a delayed onset of arthralgia and myalgia. In 1 patient weakness of the legs and skin changes in the hands during a period of some months were present 2 years prior the first medical tests; symptoms resolved without therapeutic intervention. The most important muscular symptom at disease onset was myalgia, which was present in 11/12 patients. Myalgia was permanent in 7/11 patients and exercise-induced in 4/11 patients. Paresis was absent in 1 patient, mild (MRC dyspnoea index 2) in 3 and severe (MRC dyspnoea index 3–7) in 7 patients. One patient was initially bedridden. Dyspnoea was mild in 3 patients and severe in 5 patients. One of these patients developed severe respiratory failure requiring mechanical ventilation within 4 weeks. Radiological findings of bilateral fibrosis especially of the lower parts of the lung preceded the onset of dyspnoea and the decrease in carbon monoxide diffusion. Other symptoms are shown in Table 1.

Muscle biopsy revealed interstitial myositis in 5/11 patients, while the other 5/11 patients had perifascicular atrophy with few mononuclear, perimysial infiltrates, and 1 patient had diffuse polymyositis. Immunohistochemical examination showed a clear predominance of CD-4$^+$ cells. No MAC deposits were found in the epithelial cells. Microtubular inclusions could not be demonstrated by electron microscopy in any patient.

Clinical course and outcome

Selected characteristics and outcome of the study population are shown in Table 2.

The mortality rate was 8 % (1/12 patients) during the mean 66 months observation period. This patient (Table 3, patient 2) died from respiratory failure due to severe lung fibrosis with the radiological findings of a honey-comb-lung. At that time, the muscle function tests were normal. Pulmonary function had improved

Table 1 Symptoms and selected laboratory results of the 12 anti-Jo-1-positive patients at disease onset

	Number of patients with symptom (%)
Symptom	
Myalgia	11 (92)
Paresis	11 (92)
Arthralgia	8 (66)
Dyspnoea	8 (66)
Fever	5 (41)
Raynaud's phenomenon	4 (33)
Mechanic's hands	3 (25)
Dysphagia	3 (25)
Weight loss	2 (16)
Nephrotic syndrome	1 (8)
Epileptic seizure	1 (8)
Sicca syndrome	1 (8)
Signs and laboratory results	
Antinuclear antibodies	4 (33)
Abnormal echocardiography	2 (16)
Lung fibrosis on chest CT	9 (82)

Table 2 Selected characteristics and outcome of myositis patients with anti-Jo-1-autoantibodies

No.	Follow-up period (months)	Myositis Score [6] at onset	Myositis Score [6] at end	CK-Nac at onset	CK-Nac at end	EMG-SPA at onset	EMG-SPA at end	MRC dyspnoea index at onset	MRC dyspnoea index at end	Lung x-ray (CT)	Skin changes	Arthralgia
1	65	17	31	8300	1260	+++	0	3	1	unchanged	unchanged	improved
2	56	29	33	418	25	0	0	2	7	severe worsening		improved
3	108	30	33	2058	130	0	0	2	1	unchanged	improved	
4	59	33	33	1113	1681	+	+	1	1	unchanged		improved
5	50	30	33	1902	154	0	0	1	1	unchanged		
6	52	4	25	2390	49	++	0	5	3	improved	worse	improved
7	127	*	*	2298	265	++	+	4	1	unchanged		worsened
8	56	22	32	3071	54	+	0	2	1	unchanged		improved
9	78	27	33	4870	65	+++	0	1	1	unchanged	unchanged	
10	52	**	27	268	12	0	0	7	4	improved		improved
11	48	19	22	1800	47	+++	0	6	4	unchanged		improved
12	46	8	28	1330	102	++	0	1	3	unchanged		unchanged

* not done because of coincident multiple sclerosis with spastic tetraparesis
** not done because of severe dyspnoea due to alveolitis, requiring mechanical ventilation
CK creatine kinase [U/l]; *EMG* electromyogram; *SPA* spontaneous pathological activity; *MRC* Medical Research Council

initially, following glucocorticoid (GLC) treatment, and remained stable with no symptoms of dyspnoea until three months before death. Cyclophosphamide (CYC) treatment, which was started at the time of referral to our department, was unsuccessful.

At the end of the follow-up period, muscle function ("Functional grading scale" of Clarke [6]) had improved in all patients as compared with the initial presentation. Muscle function was normal in 6/12 patients, associated with mild deficits in 1 patient, and with moderate changes in 5 patients. CK activity levels returned to normal (< 80 U/l) in 6 patients, and stayed slightly elevated in 4 patients. In one patient without muscle symptoms, CK activity remained unchanged (patient 4), another patient (patient 1) had no muscle symptoms, if his CK serum levels were lower than 3000 U/l. In this patient, normalisation of CK activity was achieved by azathioprine (AZA) only, while other drugs (CYC, cyclosporine-A (CsA), methotrexate (MTX)) resulted in a decrease of CK activity to 1500 U/l, but not to normal (see also Table 3).

Pulmonary function worsened constantly in the one patient who died. Carbon monoxide and blood gas measurements improved partially in 7/12 patients and normalised in 4/12 patients. Regarding subjective pulmonary function 5/12 patients were asymptomatic, 5/12 showed dyspnoea and 1/12 suffered from chronic cough. Radiological findings worsened constantly in the one patient only, with fatal outcome.

Despite improvement of muscle and pulmonary function, one patient (Table 3, patient 3) developed severe deforming arthropathy of the hands with joint subluxations. Another patient (Table 3, patient 7) suffered from severe shoulder joint destruction.

During follow-up, all patients received glucocorticoids. In 7 patients (Table 3, patients 1, 3, 4, 6, 8, 10, 12) treatment with 2 or more additional drugs was necessary because of side effects or lack of efficacy (up to 5 different medications in one patient).

At the end of study, 7 patients were receiving a combination treatment with 2 immunosuppressive drugs [GLC + MTX: 3 patients (Table 3, patients 1, 3, 8); GLC + intravenous immunoglobulins (IVIg): 2 patients (Table 3, patients 6, 10); GLC + AZA: 1 patient (Table 3, patient 4); GLC + CYC: 1 patient (Table 3, patient 2)]. 4 patients were on monotherapy [2 GLC (Table 3, patients 11, 12), 1 MTX (Table 3, patient 5), 1 AZA (Table 3, patient 7)]. Complete remission without the need of further immunosuppressive treatment was achieved in 1 patient (Table 3, patient 9).

GLCs produced at least a partial effect in all patients. The range of the minimum efficacious dosage levels was between 7.5 mg to 40 mg prednisone per day. Lowering of the dosage below the respective minimum level led to a relapse, which in 3 patients could not be stopped merely by a re-increase of the GLC dosage. Response to

Table 3 Treatments of myositis patients with anti-Jo-1-antibodies

No.	GLC[1]	MTX	AZA	CsA	CYC	IVIg	Complications
1	20 mg/d (65 months)	⑤[2] 15 mg/week (24 months)	① 150 mg/d (4 months)	④ 150–300 mg/d (3 months)	② 100 mg/d (2 months)	③ 1 course of 2x40 g 2 courses of 5x40 g	liver enzymes ↑ (AZA side effect) osteoporosis thoracic vertebra fracture
2	7.5 mg/d (21 months)	n. d.	n. d.	n. d.	① 150–200 mg/d (4 weeks)	n. d.	fatal outcome due to respiratory failure
3	15 mg/d (73 months)	② 20 mg/week (23 months)	① 100 mg/d (3 weeks)	n. d.	n. d.	n. d.	leucopenia (AZA side effect) Non-Hodgkin-Lymphoma
4	10 mg/d (59 months)	① 15 mg/week (5 months)	② 100–175 mg (26 months)	n. d.	n. d.	n. d.	
5	12.5 mg/d (38 months)	① 10 mg/week (36 months)	n. d.	n. d.	n. d.	n. d.	
6	10 mg/d (52 months)	① 10–15 mg/week (24 months)	n. d.	n. d.	② 100 mg/d (6 months)	③ 6 courses of 5x30–40 g (10 months)	osteoporosis, diabetes
7	10 mg/d (127 months)	n. d.	① 100 mg/d (26 months)	n. d.	n. d.	n. d.	osteoporosis, pneumonia
8	10 mg/d (53 months)	② 10 mg/week (27 months)	① 100–150 mg/d (28 months)	n. d.	n. d.	n. d.	
9	10 mg/d (24 months)	① 10 mg/week (41 months)	n. d.	n. d.	n. d.	n. d.	
10	7.5 mg/d (52 months)	① 10 mg/week (17 months)	n. d.	n. d.	② 50–100 mg/d (22 months)	③ 9 courses of 5x30–40 g (13 months)	leucopenia (CYC side effect)
11	7.5 mg/d (48 months)	① 100–150 mg (4 months)	n. d.	n. d.	n. d.	n. d.	pneumonia
12	10 mg/d (46 months)	n. d.	② 75 mg/d (39 months)	n. d.	① 25 mg/d (3 weeks)	n. d.	haemorrhagic cystitis (CYC side effect) liver enzymes ↑ (AZA side effect) osteoporosis

⋯ latest (partially) effective treatment

[1] lowest dose of prednisone for maintaining effects

[2] ①–⑤ chronological order of treatment;

GLC glucocorticoids; *MTX* methotrexate; *AZA* azathioprine; *CsA* cyclosporine-A; *CYC* cyclophosphamide; *IVIg* intravenous immunoglobulins; all drugs (apart from IVIg) were taken orally

CYC treatment was good in 1/4 patients (Table 3, patient 10) and insufficient in 2 patients (Table 3, patients 1, 6). 1 patient showed a twofold increase of CK levels following the commencement of CYC treatment (Table 3, patient 1), another one developed haemorrhagic cystitis after 3 weeks of low dose therapy (Table 3, patient 12). IVIg treatment was successful in 2 patients who had not responded to CYC treatment (Table 3, patients 1, 6) and in one patient, who had to stop CYC treatment owing to severe leukopenia (Table 3, patient 10). Photopheresis was ineffective in 2/2 patients.

Relapses during GLC withdrawal occurred in all but one patient, relapses during continuous immunosuppressive medication in 5/12 patients.

Severe drug related side effects occurred in 7 patients. Four patients (Table 3, patients 1, 6, 7, 12) developed severe osteoporosis (1 with fracture of a thoracic vertebra, 1 with chronic pain requiring opioid medication). Two patients (Table 3, patients 7, 11) developed pneumonia (1 with *Pneumocystis carinii* infection requiring mechanical ventilation). Toxic hepatopathy was found in 2 patients (Table 3, patients 1, 12), severe leucopenia in 2 patients (Table 3, patients 3, 10), and haemorrhagic cystitis in 1 patient (Table 3, patient 12). In 1

patient an anaplastic non-Hodgkin-lymphoma was detected after 98 months of treatment (Table 3, patient 3).

Discussion

The present study indicates a good, but not complete response to immunosuppressive treatment in most patients with polymyositis associated with anti-Jo-1 antibodies. All but one patient needed long-term immunosuppressive treatment. Corresponding findings have been published by other authors [13, 18].

Although most of the patients required additional immunosuppressive agents, GLC is the only drug with at least a partial effect in all of our patients. But in most patients requiring immunosuppressive treatment, a decrease of prednisone below 7.5 mg/day could not be achieved. The findings also emphasize a slow and careful GLC tapering as one of the most crucial elements in the treatment of patients with the anti-Jo-1 syndrome. The high number of different drugs used in each single patient indicates the challenge in treating patients with the anti-Jo-1 syndrome. Our data show that the individual response to treatment with different immunosuppressive medications is not predictable. Our relapse rate is higher than that published by Phillips et al. [20], who found only 13 % of relapses following GLC tapering in patients with overlap syndromes. In patients presenting with only polymyositis or dermatomyositis, they found a relapse rate of 31 % and 22 %, respectively.

MTX in combination with GLC alone improved muscle and pulmonary function in 3/6 patients. Up to now, one case report with successful treatment of anti-Jo-1-syndrome with MTX has been published [9]. Following the results of another study, the combination of oral MTX and AZA seems to be superior to either drug alone [23]. In view of the few and well-known side effects of this drug, which is now used in almost all rheumatic diseases [2], this substance seems to be worthwhile to be tried.

Oral application of CYC was not effective in 4/5 patients. In one patient, a significant worsening of symptoms occurred. Its use in polymyositis and dermatomyositis has not been proven in controlled studies. In one study, 4/7 patients with refractory polymyositis improved [11], whereas in another study it was inefficacious in 10/12 patients [7]. In patients with polymyositis and interstitial lung disease, CYC was not efficacious in 2 patients [4]. Another study showed the efficacy of intravenous pulse CYC in 6 patients with rapidly progressive interstitial lung disease due to PM and other connective tissue diseases [24].

CsA has been tried without success in one patient, only. A series of 8 patients with interstitial pneumonitis and polymyositis, in which addition of CsA to other immunosuppressive agents (MTX, CYC) was successful, was published by another group [15]. Another study (36 patients with polymyositis and dermatomyositis) showed the efficacy of both CsA and MTX, when added to a tapering dose of GLC [22]. Two reasons may be responsible for the treatment failure in our patient. First, we used CsA in addition to GLC, only. There is a case report, in which the combination of MTX and CsA was more effective than AZA and MTX alone [17]. Second, it was used late in the individual course of the disease. It has been argued that CsA might be effective in the early stages of the disease, exclusively [10].

IVIg have been shown to be a promising treatment option in our patients with refractory anti-Jo-1 syndrome. All 3 patients, who were treated with IVIg (2 g/kg body weight), responded. A number of studies have shown IVIg treatment to be useful in refractory inflammatory myopathies [5, 8]. In anti-synthetase syndromes, results of controlled studies testing IVIg treatment have not been published so far.

After the follow-up period of our study, mycophenolate was effective to stabilize remission in a patient with the history of treatment failure to CYC, MTX and GLCs. In this patient, remission was induced by IVIg (Table 3, patient 6). Promising results with tacrolimus [19] may be a treatment option for patients with interstitial lung disease due to the anti-Jo-1-syndrome, but was not tested in our cohort.

In contrast to the good remission of muscle symptoms, pulmonary symptoms responded to a lesser degree. In one patient, interstitial lung disease progressed to respiratory failure in contrast to the complete remission of musculoskeletal symptoms. The main risk of lung fibrosis is the rapid onset of decline of respiratory function.

In summary, the outcome of patients with polymyositis and pulmonary involvement in our cohort was better than reported in the literature. The mortality rate was 8 % and deterioration of pulmonary function was found only in the patient with lethal outcome. Arsura et al., performing a Medline survey, found a mortality rate of 40 % [4]. The reason for these contrasting results may be the inclusion of patients with pulmonary symptoms and radiological signs of fibrosis, but without histologically proven fibrosis, whereas in the study of Arsura only patients with histologically proven lung fibrosis were included. This indicates that early and consistent monitoring and therapy are necessary to prevent a fatal outcome.

On the other hand, the high rate of severe, potentially life-threatening complications in our study shows that only a highly individualized therapy is able to manage patients with the anti-Jo-1-syndrome.

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