

Long-term follow-up of sporadic inclusion body myositis treated with intravenous immunoglobulin: a retrospective study of 16 patients

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Abstract

Objectives

Previous studies of intravenous immunoglobulin (IVIG) treatment in sporadic inclusion body myositis (sIBM) have yielded conflicting results. Here, we have undertaken a retrospective assessment of the long-term effects of IVIG in our sIBM cohort.

Methods

Sixteen sIBM patients, treated with a mean of 10 IVIG infusions and followed up for a mean period of 23 months, were identified. Six sIBM patients treated with other drugs were used as an internal control group. Serial data on manual muscle testing (MMT), laboratory parameters and patients' subjective assessment were collected.

Results

Serial MMT scores were available in 14 IVIG treated patients. Two of these patients improved more than 20% in MMT from baseline up to the third IVIG infusion. One of six patients in the control group showed a similar MMT improvement during the first six months. Improved swallowing function was reported by three IVIG-treated patients, but none of the controls. The serum levels of creatine kinase fell more than 20 % after the first IVIG infusion in 7/16 IVIG-treated patients, but this improvement was not sustained during the follow-up period.

Conclusion

IVIG treatment appears to have short-term beneficial effects on muscle strength and dysphagia in some few sIBM patients, but these effects are not sustained over time.

Key words

sporadic inclusion body myositis (sIBM), intravenous immunoglobulin (IVIG)

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Introduction

Sporadic inclusion body myositis (sIBM) is the most common disabling inflammatory myopathy in patients above the age of 50 (1). The disease has a slowly progressive course and may over time result in incapacitating muscular weakness and atrophy. Dysphagia is a frequent symptom, occurring in at least 60% of patients (2). The aetiology of sIBM is poorly understood; genetic factors, ageing and environmental triggers might all be contributing factors (3, 4). The diagnosis of sIBM is based on clinical manifestations and typical histological findings on muscle biopsy. Although definite signs of immune-mediated inflammation in muscle biopsies are often present, sIBM generally responds very poorly to immunomodulating therapies (5). Intravenous immunoglobulin (IVIG), a fractionated blood product, is possibly an exception. IVIG is utilised in the treatment of a wide spectrum of immune-mediated diseases (6, 7), but its mechanism of action is still not completely understood (8, 9). Early uncontrolled trials indicated efficacy of IVIG in sIBM, but later double-blind placebo-controlled studies failed to show significant beneficial effects on sIBM patients, except from marginal benefits on dysphagia (10,11). Since the controlled studies were undertaken on a small number of patients and had an observation period of only 3–6 months, we decided that it was of interest to analyse the long-term effects of IVIG treatment in our group of Norwegian sIBM patients. Our objective was to do a retrospective assessment of muscle strength, swallowing function and laboratory parameters in sIBM patients receiving IVIG. Since the study was based on retrospective chart review, it was not placebo-controlled, but for comparison, we have included data on a group of sIBM patients not treated with IVIG.

Materials and methods

Patient group

We have recently established a database with data on the 240 idiopathic inflammatory myopathy (IIM) patients seen at our tertiary referral hospital from 1960–2007. According to the

diagnostic criteria of Griggs *et al.* (12), 36 of these IIM patients had a probable or definite sIBM. Retrospective chart review showed that 16 of these sIBM patients (10 males and six females) received IVIG treatment at our hospital. The clinical indication for starting IVIG treatment was declining muscle strength and/or severe dysphagia. In addition, we identified six other sIBM patients treated with other drugs who had long-term follow-up data. These six patients were included in the study as an internal control group.

Patient assessment

Muscle strength was evaluated by the Manual Muscle Test (MMT) developed by Kendall (13, 14). MMT measures the isometric force exerted by a muscle group at a specific angle, the resistance being applied by the examiner. The muscle strength in individual groups is scored on a 0–10 point scale. At each evaluation, the physiotherapists examined a set of muscle groups on the right and left side of the body. The same muscle groups were assessed every time in each individual patient. The total number of muscle groups assessed was not the same in all patients, but varied from five to ten. The MMT scores from the right and the left side were added and divided by two, giving a maximum total MMT score between 50 and 100 MMT total. Since the quadriceps femoris muscles are the most commonly affected muscle group in sIBM, we decided to look at the scores of this muscle separately (MMT quadriceps). The analyses of the MMT data were done blinded to clinical information.

A change of more than 20% in the MMT total and/or an increase or decrease of two or more gradients in the MMT quadriceps scores, were considered clinically significant.

The other parameters reviewed were; (1) dynamic studies of the oesophagus by barium x-ray. (2) Serum creatine kinase (CK) levels and ESR measured at baseline and then before each IVIG infusion. A decrease or increase of 20% or more in CK or ESR-levels was regarded as significant changes. (3) The patients' self-reported dysphagia and

Competing interests: none declared.

muscle strength prior to the onset of IVIG treatment and during the follow up period.

IVIG treatment

The standard treatment protocol for IVIG was to give a total dose of 2g/kg body weight over three or five days. Two patients received a reduced dose of 1g/kg because of side-effects (headaches during infusion). According to the protocol, IVIG infusions should be given either monthly or once every third month. The treatment was tailored according to the perceived need of each individual patient (*i.e.* changed treatment interval or stopped infusions).

Statistical analysis

The OpenEpi statistical software program was utilised for data analysis. Chi-squared or Fischer exact analysis was used to compare results in the IVIG-group compared to the control group. A *p*-value less than 0.05 was regarded as statistically significant.

Results

Patients' characteristics

The mean age at commencing IVIG treatment was 66.8 years with a mean sIBM duration at start of treatment of 5.3 years (0.5–15 years) (Table I). The mean number of IVIG infusions was 10 and mean follow-up time was 23 months (Table I). The number of infusions given to each patient, and the interval between the treatments are indicated by the arrows in Figure 1a. Twelve of the 16 patients in the IVIG group received corticosteroids prior to commencing IVIG treatment and six of these continued this treatment simultaneously with the IVIG-infusions (with at a mean daily prednisolone dose of 10mg) One patient received infusions of methylprednisone before the IVIG. Four patients were treated with other immune-modulating drugs before IVIG and two received other treatments during the IVIG period (Table I). Three of the 16 patients had serum autoantibodies (P2 and P15 had anti-SSA, while P7 had anti-RNP). Both patients with anti-SSA antibodies had primary Sjögren's syndrome.

The control group had a mean age of 63.4

Table I. Demographics of 16 sIBM patients treated with IVIG.

Patient ID	Sex/Age	Disease duration (years)	Baseline MMT	IVIG Infusions (N)	follow up time (months)	Previous Treatment	Treatment during IVIG
1	M/ 69	5	54/90	3	15	CS	CS
2	M/65	0.5	75/90	5	20	CS	No
3	F/65	15	80/90	16	29	CS	No
4	M/75	5	63/90	20	48	None	No
5	F/74	3	79/90	3	15	CS, AZA	No
6	F/53	6	78/90	5	14	CS	No
7	F/58	6	80/90	12	41	None	No
8	M/77	14	68/100	5	12	CS	No
9	M/66	1	81/90	8	27	CS, MTX	CS, MTX
10	M/71	8	63/90	11	18	CS	No
11	M/45	2	73/90	13	33	CS	CS
12	M/68	3	64/90	5	15	None	No
13	F/54	4	63/100	25	35	CS, ++*	CS, MTX
14	M/77	3	63/80	4	13	CS	CS
15	F/80	8	53/60	6	11	CS	CS
16	M/71	0.5	42/80	12	24	CS, Aza	CS

CS: corticosteroids; AZA: azathioprine; MTX: Methotrexate; (*++: Anakinra and rituximab).

Table II. Overview of the control group.

ID	Sex/Age	Baseline MMT	Follow-up time (months)	Therapy	Oesophagus dysmotility	Self-reported swallowing function
C1	M/61	85/90	19	AZA, MTX	Mild	Mild dysphagia
C2	F/71	71/90	36	Cs	Severe	Severe dysphagia
C3	M/49	78/90	29	Cs, MTX	Moderate	asymptomatic
C4	M/47	95/110	41	Cs, MTX	No	asymptomatic
C5	F/73	53/90	26	Cs	Mild	Moderate dysphagia
C6	F/71	53/90	42	Cs, AZA	Severe	Severe dysphagia

*Cs: Corticosteroids; *MTX: Methotrexate; *AZA: Azathioprine.

years and a mean follow-up time of 34.2 months (20–47 months) (Table II). Five of the control patients were treated with prednisolone (at a mean daily starting-dose of 38.5mg). Two of these patients received Methotrexate concomitantly, while one used azathioprine. The last of the six control patients was first treated with methotrexate in monotherapy, but was later switched to azathioprine.

Manual muscle test

Data from at least three MMT assessments performed during the IVIG treatment period was available in 14 patients (Fig. 1A). In two of these patients (P13 and P16), a more than 20% improvement in MMT Total scores and a two gradient improvement in MMT quadriceps scores was observed early in the treatment period. These effects were, however, not sustained to the end

of the follow-up period. One patient (P3) improved two gradients in MMT quadriceps scores and this improvement was partly sustained throughout the observation period.

At the end of the follow-up period, one of the patients (P13) had a more than 20% decrease in the total MMT score compared to baseline. Two other patients (P11 and P14) had more than two gradient decreases in their MMT quadriceps score compared to baseline (Fig. 1A).

Compared to the values at baseline, one of the six control patients (C5) displayed a more than 20% improvement in the total MMT and a two gradient improvement in the MMT quadriceps score at the end of follow-up (Fig. 1B). The remaining five control patients showed no significant MMT changes throughout the observation period.

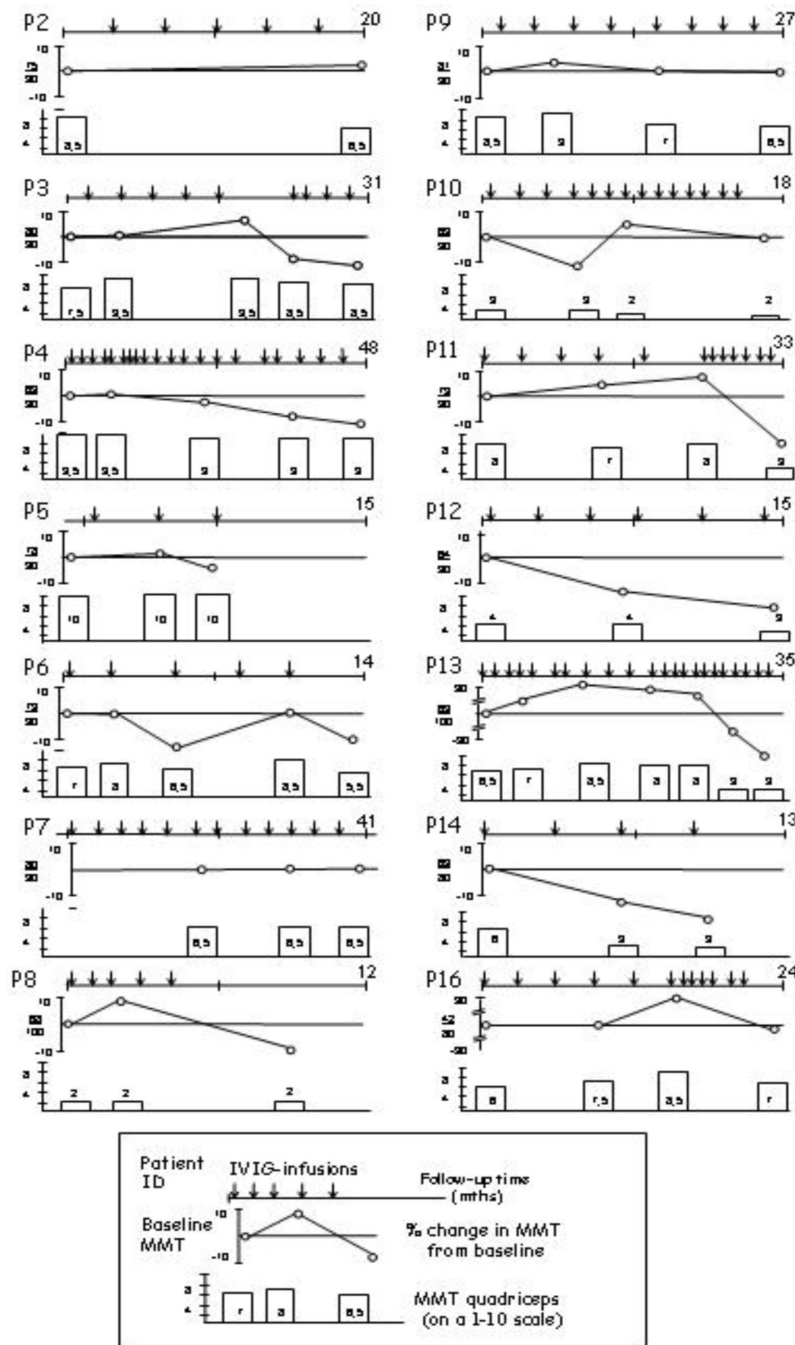


Fig. 1A. Longitudinal development of muscle strength, evaluated by the Manual Muscle Test (MMT), in 14 sIBM patients treated with IVIG. The upper part of each panel shows the number of IVIG infusions (arrows) and the total follow-up time. The middle part shows the baseline total MMT and the individual total MMT scores obtained during the treatment period. The lower part of each panel depicts the corresponding MMT quadriceps scores.

Oesophagus dysmotility

Fourteen of the IVIG treated patients were examined with radiological dynamic studies of the oesophagus. Severe dysmotility was found in five of these patients, while seven had mild to moderate findings. Normal oesophagus motility was only found in two patients. Two of the six patients in the control

group had marked dysmotility and corresponding severe symptoms. Three of the IVIG treated patients (P9, P12 and P16) reported subjective improvement on swallowing function during follow-up compared to none in the control group. Three of the IVIG treated patients with severe dysphagia (P4, P8 and P10) received surgery or botox-injections

during the follow-up period. Repeated dynamic studies were undertaken in two patients (P4 and P10), both of these showed a worsening of dysmotility over time, despite IVIG treatment.

Serum creatin kinase (CK) and ESR

Baseline measurements of serum CK were available in all the 16 IVIG treated patients; the CK-levels varied between 90 and 3696 mg/l (mean 894 mg/l). A decrease of more than 20% in CK-level was observed in 7/16 patients up to the second IVIG infusion (data not shown). One of the patients with significant CK-reductions concomitantly improved in MMT score (P13), while two others (P12 and 14) got worse (Fig. 1A). CK data from the end of follow-up were available in 11/16 patients, all 11 had higher CK-levels at the end of follow-up than at baseline.

A similar trend was observed in the control group; an initial reduction in CK-levels and then a gradual increase to baseline (or higher) (data not shown).

ESR levels were between 8–45 mm (mean 17) before commencing IVIG treatment. Three patients had a more than 20% reduction in ESR levels (P2, P5 and P15) before the second IVIG infusion. In the control group, ESR levels varied between 13 and 80 (mean 36). No significant differences in CK and ESR between the two groups were seen (data not shown).

Prior use of corticosteroids

Information on the use of oral corticosteroids prior to the IVIG treatment was available in fifteen of the 16 IVIG treated patients (Table I). We found that three of the 13 (23%) sIBM patients who had used CS prior to IVIG had responded with decreasing CK-levels and subjective improvement of muscle strength. Interestingly, two of these three CS responders (P13 and P16) later responded to the IVIG treatment.

Safety

The only side effects reported were mild to moderate headaches during and after the IVIG infusions. No serious viral infections, major cardiac events or neurological complications were noted during the treatment.

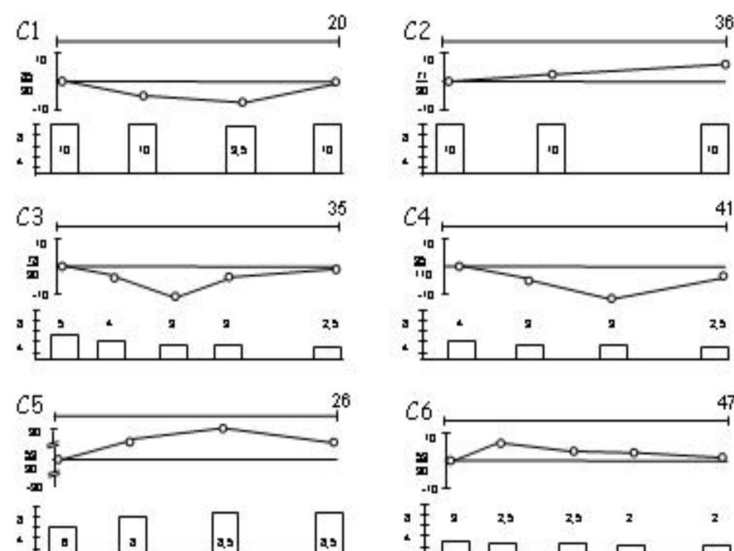


Fig. 1B. Longitudinal development of muscle strength, evaluated by the MMT test, in six sIBM patients treated with other immune-modulating therapies.

Discussion

The need for better management of sIBM is imperative. While most immunosuppressive agents utilised in other inflammatory myopathies have failed, it is still debated whether IVIG treatment may be useful in sIBM. To help clarify this issue, we have performed a retrospective analysis of our sIBM patients treated with IVIG. Our main findings are; (1) Two of 14 patients receiving IVIG improved in limb muscle strength early in the treatment period, but this effect was not sustained to the end of the follow-up. (2) Only one of the 14 patients displayed significant worsening of muscle strength during the observation period. (3) Improved swallowing function was reported by three IVIG treated patients, but none in the control group. (4) Overall, we did not find any differences in MMT, CK-levels or ESR between the IVIG treated group and a control group treated with other immune-modulating drugs.

Since our patients were treated according to perceived need, rather than standardised protocols, the time intervals, treatment regimes and follow-up time differed between the patients. Despite these inconsistencies, we still believe that our “real life”, time-course data adds more information on the potential effects of IVIG in sIBM. One of our key observations was that IVIG, seemed to stabilise limb muscle strength in nearly all the patients throughout the whole observation period. Importantly, we

found that the six control patients (on other immune-modulating drugs) had similarly stable MMT scores. It is thus possible that the relatively preserved MMT scores, rather than being treatment effects, simply show that sIBM is a slowly progressive disease. An alternative explanation is that many different immune-modulating drugs, including IVIG and methotrexate, may actually slow down the progression rate of the disease. No clear evidence for such an effect has been shown in previous studies, but they have all been of shorter duration (10, 11, 17).

Data on the response to previous treatment with oral corticosteroids was available in 13 of the IVIG treated patients. Only three of these patients displayed decreased ESR and CK-levels and reported subjective improvement of strength when treated with oral corticosteroids. Interestingly, two of these corticosteroid responders were the same two patients (P13 and P16; Table I) that later showed a good initial response to treatment with IVIG. We did not, however, find any correlation between IVIG effects on dysphagia and previous steroid responses. Overall, we believe that our observations strengthen the notion that IVIG, in general, is not very effective in sIBM, but that it may be an option in selected patients with severe dysphagia and possibly also in patients who have short disease duration and ongoing inflammatory activity in their affected skeletal muscle groups.

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