Intravenous immunoglobulin in the treatment of sporadic inclusion body myositis: time for new evidence?

Sir,

Sporadic inclusion body myositis (s-IBM) is the most commonly acquired myopathy in patients over the age of fifty. The clinical course of s-IBM is frequently slow, yet relentless. Pathogenesis is still blurred, and no drugs have been specifically approved to treat this condition yet. Since inflammation is thought to play a major role in the disease, immunoagents, including intravenous immunoglobulins (IVIG), have been used as therapeutic attempts, with little evidence of efficacy. Given the economic burden of IVIG and their recent worldwide shortage, attention should be paid to their careful and appropriate use. We evaluated the evidence of efficacy of IVIG in the treatment of s-IBM through a comprehensive analysis of existing literature. We retrieved 226 results from PubMed/MEDLINE database: after initial screening, we selected ten relevant articles which were studied in detail. The use of IVIG in s-IBM has been variously addressed in the past. Table I summarises the main characteristics of the randomised clinical trials (RCTs) and case reports. The two RCTs conducted failed to find any objective effect on muscle strength, dysphagia, and electromyographic findings, with only a moderate effect on the subjective Neuromuscular Symptom Score (5). Moreover, in a small *in vitro* study, Dalakas *et al*. showed that muscle biopsies of people treated with IVIG and prednisone had fewer necrotic fibres compared to those receiving prednisone alone, but that this finding had no clinical correlation (4). Of note, in two different studies, Dalakas *et al*. reported that: (i) a fraction of patients treated with IVIG had a functionally relevant improvement that was lost when patients switched to prednisone-only treatment; (ii) half of the patients treated with IVIG experienced an increased endurance, compared to none in the prednisone-only group. These positive, albeit temporary, results agree with the outcome of different case reports, which show promising, even quite striking, outcomes relative to muscle strength, dysphagia and serum values (7-10). Many factors can contribute to this apparent variability in results. In particular, timing may play a crucial role: as observed by Foreman *et al*. (8), patients who had favourable response initiated IVIG closer to time of diagnosis compared to those with non-responders. It is worth to consider that the retrieved stud-

Table I. Clinical trials, audit, case series, case report. Results were retrieved from PubMed/MEDLINE database on January 26, 2024. All randomised clinical trials failed to show any effect of IVIG on muscle strength, dysphagia, serum values. Of note, one third of the patients in the cross-over study by Dalakas *et al*. had a great improvement during IVIG and deteriorated when passing to placebo. Various case reports and case series showed promising results of IVIG.

Reference	Study type	Number of patients	IVIG dose	Outcome measures	Key results	Study weakness
Amato *et al*. (1)	Uncontrolled open label study.	Nine	Four patients: 2 g/kg/mo. per three months. Five patients: 2 g/kg followed by maintenance doses at various intervals.	MMT; functional disability scores; CK serum levels.	No effects. Two patients reported subjective improvement in fatigue.	Uncontrolled study; low number of patients; no control group; infusion protocols varied amongst patients; four patients received IVIG + other immunotherapies
Dobloug *et al*. (2)	Retrospective case control study.	Twenty-two. Sixteen: IVIG. Six: other drugs.	variable	MMT; swallowing function; CK serum values; patient self-reported dysphagia and muscle strength.	No effects. Improved swallowing function reported by three patients treated with IVIG.	Retrospective study; number of muscle assessed was not the same in all patients; infusion protocols varied amongst patients; some patients in IVIG group received steroids or other immunosuppressant drugs.
Dalakas *et al*. (3)	Randomised, double blind, placebo controlled, cross-over study.	Nineteen.	2 g/kg/mo. per three months	MMT; quantitative swallowing studies; disability scores.	No effects. Positive, non-significant, trend for MMT on IVIG group. Six patients improved by more than 10 MRC points and deteriorated when crossing over to placebo	Some patients in IVIG group received steroids.
Dalakas *et al*. (4)	Randomised, double blind, placebo-controlled study.	Thirty-six. Nineteen: IVIG+ prednisone; Seventeen patients: placebo + prednisone.	2 g/kg/mo. per three months	Quantitative Muscle Strength testing; MMT; assessment of T cells and necrotic fibres on repeated muscle biopsies.	Half of the patients in IVIG group reported increased endurance and ability to better perform some activities of daily living. Number of necrotic fibres was reduced in the IVIG randomised group, but the reduction was not of clinical significance.	-
Walter *et al*. (5)	Double blind, placebo-controlled, crossover study.	Twenty-two.	2 g/kg/mo. (or placebo) per six months	MMT; EMG; patient's own assessment of improvement.	Moderate effect of IVIG on NSS, no effects on muscle strength or in electromyographic findings.	-
Zschüntzsch *et al*. (6)	Retrospective case-control study.	Ten. Five: IVIG+ prednisone; five: prednisone alone.	2 g/kg/mo. per three months	Expression of inflammatory and degeneration markers in muscle biopsies.	No differences between IVIG + corticosteroids *vs*. corticosteroids alone.	Retrospective study; low number of patients.

Reference	Study type	Number of patients	IVIG dose	Outcome measures	Key results	Study weakness
Cherin *et al*. (7)	Case series	Four	variable	Dysphagia evaluated by oesophageal manometry.	Dysphagia was ameliorated in all patients.	Low number of patients; infusion protocols varied amongst patients; no control group.
Foreman *et al*. (8)	Case series	Fifteen	NA	NA	Eighty-three percent of patients treated for more than 2 months had favourable outcome, compared to none in those with shorter course; Patient with favourable outcome started IVIG earlier compared of non-responders.	Retrospective study; No clear definition of "favourable response"; No control group.
Soueidan *et al*. (9)	Case series	Four	2g/kg/mo. per 2 months	MMT, functional improvement, CK serum level	Three patients had functional improvement and increased strength; Three patients reported subjective improvement in fatigue. CK serum level dropped after first infusion.	Low number of patients; no control group; one patient received steroids.
Recher *et al*. (10)	Case report	One	0.3 g/kg/day given on two consecutive days as a monthly cycle.	MMT	Subjective amelioration of muscle strength; trend to amelioration on objective muscle strength testing, Normalisation of CK serum levels; Improvement on muscle MRI.	Single case

IVIG: intravenous immunoglobulins; MMT: manual muscle testing; mo.: month; MRC: medical research council score; MRI: magnetic resonance imaging; NSS: Neuromuscular Symptom Score; EMG: electromyography; NA: not available.

ies are overall heterogenous regarding time from diagnosis, disease duration, treatment regimes, concomitant drugs, and outcome measures, thus a definitive conclusion concerning the effect of IVIG on s-IBM remains elusive. Since there is no statistical evidence for the use of IVIG to improve strength, dysphagia or functional outcome, a recent consensus statement advice against the use of this therapy in s-IBM. However, it may be possible that only a small number of the patients respond to IVIG as reported in the various case reports; since no biomarkers are currently available to predict the outcome, it is impossible to identify those patients who may benefit from the treatment. In this regard, future studies with a higher number of patients, designed to objectively measure various outcome, and also aimed at evaluating the existence of distinctive characteristics related to IVIG response, are advisable in order to gather new evidence, and increase the appropriateness of the use of IVIG in s-IBM. Meanwhile, we believe that the use of IVIG in clinical practice should be approached with caution considering the potential adverse events and the economic burden of such medicines.

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