Subcutaneous immunoglobulin in treating inflammatory neuromuscular disorders

Min-Suk Yoon, Ralf Gold and Antonios Kerasnoudis

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Abstract

Objective: Intravenous immunoglobulin administration has long been used in the treatment of autoimmune neuromuscular disorders. Immunoglobulins may be administered by intramuscular, intravenous or subcutaneous routes.

Methods: This is a report on the long-term clinical follow up of six patients with inflammatory neuromuscular disorders, that is, three chronic inflammatory demyelinating polyneuropathy (CIDP), one multifocal motor neuropathy (MMN), one inclusion body myositis (IBM) and one myasthenia gravis (MG), treated with subcutaneous immunoglobulins for a mean of 3.25 years.

Results: One MMN and two CIDP patients received a weekly dose of subcutaneous immunoglobulins equivalent to intravenous immunoglobulin. One CIDP patient received a 50% dose reduction, the IBM patient received a 30% reduction and the MG patient a 20% reduction. The lower dose chosen in the majority of patients was based not only on clinical effects, but also on studies of primary immunodeficiency syndromes. One patient with CIDP showed clinical fluctuation, which was successfully treated with an adaptation of the dose of subcutaneous immunoglobulins, while the remaining patients with neuromuscular disorders had a stable clinical course for 2 years. No serious side effects were observed.

Conclusions: Our results suggest that subcutaneous immunoglobulins can be an attractive alternative therapy in autoimmune neuromuscular disorders.

Keywords: chronic inflammatory demyelinating polyneuropathy, inclusion body myositis, multifocal motor neuropathy, myasthenia gravis, subcutaneous immunoglobulin

Introduction

Immunoglobulin (Ig) replacement has long been used in the treatment of a wide variety of primary and secondary antibody deficiencies. Behring and Kitasato were the first to document the efficiency of immune serum from animals on toxin-induced diseases [Behring and Kitasato, 1890], while the beneficial effect of IgG replacement was first reported in a case of agammaglobulinaemia [Bruton, 1952]. High-dose intravenous immunoglobulin (IVIg) is considered an evidence-based treatment in acute inflammatory demyelinating polyneuropathy, chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN), while positive therapeutic responses have also been reported in patients with myasthenia gravis (MG) [European Federation of Neurological Societies, 2008]. In

addition, IVIg seems to be effective in inclusion body myositis (IBM)-associated dysphagia [Dalakas *et al.* 1997; Pars *et al.* 2013].

Ig may be administered by intramuscular, intravenous or subcutaneous routes [Bonilla, 2008]. Over recent years, a renewed interest in alternative routes of Ig administration has resulted in trials comparing IVIg with subcutaneous Ig (SCIg) administration in patients with immunodeficiency syndromes with low or absent antibody production [Chinen and Shearer, 2004]. Successful SCIg administration has also been reported in patients with CIDP [Markvardsen *et al.* 2013; Bayas *et al.* 2013; Cocito *et al.* 2011], MMN [Misbah *et al.* 2011; Harbo *et al.* 2009, 2010; Eftimov *et al.* 2009; Lee *et al.* 2008], and IBM [Pars *et al.* 2013].

Correspondence to:
Antonios Kerasnoudis, MD
Department of Neurology,
St. Josef-Hospital, Ruhr
University, Gudrunstr. 56,
44791 Bochum, Germany
antonis.kerasnoudis@gmail.com

Min-Suk Yoon, MD
Ralf Gold, MD
Department of Neurology,
Ruhr University, Bochum,
Germany

We aimed to report the long-term clinical follow up of six IVIg-dependent patients with inflammatory neuromuscular disorders treated with SCIg.

Materials and methods

This study concerned a retrospective analysis of the clinical follow up in a group of patients with known inflammatory neuromuscular disorders receiving SCIg. Overall the charts of three patients with CIDP, one with MMN, one with IBM and one with MG, fulfilling the diagnostic criteria published elsewhere [Van den Bergh *et al.* 2010; Joint Task Force of the EFNS and the PNS, 2010; Needham and Mastaglia, 2007; Jaretzki *et al.* 2000], were evaluated. Due to the retrospective character of this study, no approval from the ethics commission of the local university was needed. The documentation of muscle strength was carried out by an experienced neurologist (AK) using the Medical Research Council (MRC) sum score before and every 6 months after SCIg therapy. The total MRC sum score ranges from 0 (total paralysis) to 60 (normal strength). The score is the sum of the MRC score of six muscles (three in the upper and three in the lower limbs) on both sides, each muscle graded from 0 to 5. The following muscles were examined: deltoid, biceps brachii, extensor carpi radialis, iliopsoas, quadriceps femoris and the tibialis anterior [Kleyweg *et al.* 1991]. The SCIg was administered by a portable, programmable pump (Type Crono Super PID, Canè S.r.l. Medical Technology, Rivoli, Italy) with a maximal syringe capacity of 20 ml or 50 ml.

All electrophysiological studies were performed by a board-certified neurologist (MSY). All testing was carried out while maintaining the skin temperature at 35.4°C. Motor (compound muscle nerve action potential, F-response studies) and sensory studies (sensory nerve action potential) were performed on both sides of the median ulnar nerve. Motor studies were performed in the fibular and tibial nerve and sensory studies in the sural and radial nerve. All systemic disorders or peripheral nerve diseases (e.g. carpal tunnel syndrome), which might influence the results of the electrophysiological studies, were excluded.

Results

CIDP

Patient 1: A 62-year-old woman was referred to our department in 2004 with distal weakness and

sensory deficits of both lower extremities of insidious onset. The clinical examination revealed a symmetric tetraparesis (MRC sum score 50), a stocking-glove type of hypaesthesia and absent tendon reflexes. Examination of the cerebrospinal fluid and nerve conduction studies, performed 3 months after symptom onset, were consistent with a sensorimotor demyelinating polyneuropathy, fulfilling the diagnostic criteria for CIDP [Van den Bergh *et al.* 2010].

The initial therapy consisting of intravenous corticosteroids (dosage 500 mg/day over 5 days) and five sessions of plasmapheresis was ineffective. The first IVIg treatment (2 g/kg over 3 days) resulted in a marked clinical improvement, not only of overall muscle strength (MRC sum score 56), but also of the hypaesthesia. The treatment was continued with a dose of 0.5 g/kg/4 weeks every 6 weeks and resulted in a stable clinical status for 5 years. Due to a new clinical deterioration in 2009 (MRC sum score 52), the IVIg treatment dosage was increased to 0.7 g/kg/4 weeks.

In 2010, the Ig therapy was switched to subcutaneous application because of persistent headaches during the intravenous administration. The patient received a 16% Ig formulation in a SCIg dose of 0.7 g/kg/4 weeks (360 ml infusion volume/4 weeks). Under the SCIg therapy the patient's symptoms remained stable (MRC sum score 52) for the following 2 years. In 2012 the patient was switched to 20% Ig formulation, preserving the same SCIg weekly dose, but achieving a volume reduction due to the higher SCIg formulation (288 ml infusion volume/4 weeks), and showed further stability for the next 2 years. The only side effects noted were mild swelling and redness at the injection sites during treatment initiation, which improved during the time course of the therapy (Table 1).

Patient 2

A 60-year-old man was referred to our department in 2005 because of a distal weakness, sensory deficits of both lower extremities and walk difficulty of insidious onset. The clinical examination revealed a symmetric paraparesis (MRC sum score 54), a stocking-glove type of hypaesthesia and reduced tendon reflexes. The cerebrospinal fluid examination and nerve conduction studies, performed 2 months after symptom onset, documented a sensorimotor primary demyelinating polyneuropathy.

Table 1. Flow chart showing the Ig therapy among the patients with various autoimmune neuromuscular disorders.

Disease	Duration	Onset	1 year	2 years	5 years	6 years	7 years	8 years
	Patient	Dosage/4 weeks						
CIDP	1	0.5 g/kg	0.5 g/kg	0.5 g/kg	0.7 g/kg	0.7 g/kg	0.7 g/kg	0.7 g/kg
	2	0.3 g/kg	0.3 g/kg	0.45 g/kg	0.45 g/kg	0.45 g/kg	0.45 g/kg	0.45 g/kg
	3	0.75 g/kg	0.4 g/kg	0.4 g/kg	0.4 g/kg			
MMN	4	0.4 g/kg	0.4 g/kg	0.4 g/kg				
IBM	5	0.6 g/kg	0.4 g/kg	0.4 g/kg				
MG	6	0.75 g/kg	0.65 g/kg	0.65 g/kg	0.65 g/kg	0.65 g/kg	0.7 g/kg	0.75 g/kg

The cells highlighted in grey represent the period of therapy with subcutaneous immunoglobulins. CIDP, chronic inflammatory demyelinating polyneuropathy; IBM, inclusion body myositis; MG, myasthenia gravis; MMN, multifocal motor neuropathy.

The initial intravenous corticosteroid therapy (500 mg/day over 5 days) was ineffective. The first IVIg treatment (2 g/kg over 3 days) resulted in a clinical improvement of overall muscle strength (MRC sum score 56), walk ability and hypaesthesia. The treatment was continued with a dose of 0.3 g/kg/4 weeks every 12 weeks and resulted in a stable clinical status for 1 year.

Due to bad venous status, the Ig therapy was switched in 2006 to subcutaneous application. The patient received a 16% Ig formulation in a SCIg dose of 0.3 g/kg/4 weeks (360 ml infusion volume/4 weeks). Under the SCIg therapy the patient's symptoms remained stable (MRC sum score 56) for 1 year. In January 2007 the patient showed a moderate worsening of the foot extensors on both sides with deterioration of walking, accompanied by par- and dysaesthesias of both lower extremities (MRC sum score 52). After increasing the SCIg dosage to approximately 0.45 g/kg/4 weeks (250 ml volume infusion/4 weeks), sensory and motor deficits showed an improvement (MRC sum score 56). The clinical status of the patient remained unchanged. In 2011 the patient was switched to 20% Ig formulation, preserving the same SCIg weekly dose, but achieving a volume reduction due to the higher SCIg formulation (200 ml infusion volume/4 weeks). He remained stable overall for 6 years under SCIg. The only side effects noted were mild redness at the injection sites, which improved during the time course of the therapy (Table 1).

Patient 3

A 62-year-old woman was referred to our department in 2009 with distal weakness, sensory deficits

and dysaesthesias of both lower extremities. The clinical examination revealed a symmetric tetraparesis (MRC sum score 46), a stocking-glove type of hypaesthesia of the extremities and absent tendon reflexes. The cerebrospinal fluid examination and nerve conduction studies, performed 4 months after disease onset, documented a sensorimotor demyelinating polyneuropathy.

The initial intravenous therapy with corticosteroids was ineffective, while the first IVIg treatment (1.5 g/kg over 3 days) led to a slight clinical improvement of overall muscle strength (MRC sum score 50), but not of the walk ability and hypaesthesias. Treatment was continued with a dose of (0.75 g/kg/4 weeks) every 8 weeks and resulted in a stable clinical and electrophysiological status for 1 year. Due to bad venous status, the Ig therapy was switched in 2012 to a subcutaneous application. Owing to the clinical stability, the patient received a 20% Ig formulation in a reduced SCIg dose of 6 g/week (0.4 g/kg/4 weeks) (approximately 120 ml infusion volume/4 weeks). Under the SCIg therapy the patient's symptoms remained stable (MRC sum score 50) for the following 2 years. The only side effects noted were mild redness at the injection sites at treatment initiation, which improved during the time course of the therapy (Table 1).

MMN

A 57-year-old man was referred to our department in 2012 with a distal weakness of the left hand over 14 years and the right hand over 7 years. He mentioned also an atrophy of the hand muscles but no sensory deficits. The clinical

examination revealed a drop-hand on both sides, with an asymmetric paresis of the finger and hand extensor muscles on both sides (MRC sum score 52), reduced tendon reflexes of the upper but not the lower extremities, without sensory deficits. Examination of the cerebrospinal fluid revealed a normal protein level, while the nerve conduction studies, performed 14 years after symptom onset, documented conduction blocks in the ulnar and tibial nerve. Laboratory tests revealed no monosialotetrahexosylganglioside antibodies in the serum.

The first IVIg treatment (2 g/kg/4 weeks) resulted in a marked clinical improvement of overall muscle strength (MRC sum score 56). The treatment was continued with a dose of 0.4 g/kg/4 weeks every 12 weeks and resulted in a stable clinical and electrophysiological status for 1 year. In view of the patient's working conditions and to avoid hospitalization, the Ig therapy was switched in March 2013 to a subcutaneous application. The patient received a 20% Ig formulation in a SCIg dose of 0.4 g/kg/4 weeks (120 ml infusion volume/4 weeks). Under the SCIg therapy the patient's symptoms remained stable (MRC sum score 56) for the following 9 months. The patient reported no side effects (Table 1).

IBM

A 58-year-old woman was referred to our department in 2010 with a proximal weakness of the lower extremities and a distal weakness of the upper extremities. The clinical examination revealed a moderate paresis of the quadriceps and finger flexor muscles and a slight paresis of the anterior tibial muscle (MRC sum score 52), without any sensory deficits. The nerve conduction studies documented no signs of polyradiculoneuropathy, while concentric needle electromyography in various proximal and distal muscles of the upper and lower limbs revealed a mixture of short- and long-duration complex motor unit potentials. The biopsy from the quadriceps muscle confirmed the presence of IBM.

The first IVIg treatment (2 g/kg over 3 days) resulted in a marked clinical improvement of overall muscle strength (MRC sum score 56) and walk ability. The treatment was continued with a dose of 0.6 g/kg/4 weeks every 8 weeks and resulted in a stable clinical and electrophysiological status for 1 year. To avoid hospitalization, the

therapy was switched in 2012 to SCIg. The patient received a 20% Ig formulation in a SCIg dose of 0.4 g/kg/4 weeks (8 g/week) (40 ml infusion volume/week). Under the SCIg therapy the patient's symptoms remained stable (MRC sum score 56) for the following 2 years. The only side effects reported were mild redness and swelling at the injection sites, which improved after local symptomatic therapy (Table 1).

MG

A 40-year-old woman was referred to our department in 2005 with a bilateral ptosis and diplopia that tended to increase as the day progressed. The clinical examination revealed a paresis of both eye opening and eye closure, flexors and extensors of the neck and shoulder girdle, and flexors of the hips (MRC sum score 48). The repetitive nerve stimulation of trapezoid and abductor digiti minimi muscles revealed a decremental response, while levels of acetylcholine receptor antibodies in the serum were elevated (1.2 nmol/L, reference values of our laboratory < 0.02 nmol/L).

The patient received pyridostigmine in a daily dose of 390 mg and showed a moderate improvement of the diplopia and ptosis, but not the muscle fatigue in the limbs. Diverse immunosuppressive agents were not tolerated by the patient (azathioprine 150 mg/day due to persistent nausea, cyclosporine 200 mg/day due to persistent arterial hypertension, tacrolimus 3 mg/day due to severe nausea). The first IVIg treatment 1 g/kg over 3 days (80 g over 3 days) resulted in a further clinical improvement of overall muscle strength (MRC sum score 56). The treatment was continued with a dose of 0.75 g/kg/4 weeks 60 g every 4 weeks (15 g/week) and resulted in a stable clinical and electrophysiological status for 1 year.

In 2006 the Ig therapy was switched to a subcutaneous application to avoid hospitalization. The patient received a 16% Ig formulation in a SCIg dose of 0.65 g/kg/4 weeks (12.8 g/week) (80 ml infusion volume/week). In 2012 the therapy was switched to a 20% Ig formulation, preserving the same SCIg weekly dose, but achieving a volume reduction due to the higher SCIg formulation 0.75 g/kg/4 weeks (12 g or 60 ml/week). Under the SCIg therapy the patient's symptoms remained stable (MRC sum score 56) for 8 years. No local or systematic side effects were reported (Table 1).

Discussion

This is a retrospective report on the long-term use of SCIg in various autoimmune neuromuscular disorders. Patients with neuromuscular disorders were followed up for a mean of 3.25 years. To our knowledge, literature reports on the long-term treatment of immune-mediated neuropathies with SCIg (more than 3 years) are rare [Bayas *et al.* 2013].

In view of the transition data from IVIg to SCIg, the retrospective evaluation showed that: 3/4 patients with immune-mediated neuropathies (two CIDP, one MMN) received an SCIg weekly dosage equivalent to IVIg, one CIDP patient received a 50% reduction, while the two patients with neuromuscular disorders received a 30% reduction (IBM) or 20% reduction (MG), respectively. The lower dose chosen in half of the patients was based not only on clinical effects, but also on studies with primary immunodeficiency syndromes, in which SCIg led to higher mean blood levels of IgG when compared with IVIg [Gardulf *et al.* 1995, 2006]. Regarding the clinical response after therapy, SCIg resulted in a clinical stabilization not only in 2/3 CIDP patients, but also in the IBM and MG patients over a period of at least 2 years. The MMN patient has been followed up so far for 9 months under SCIg therapy and was stable during this period. These results confirm previously reported findings that SCIg treatment may be an attractive alternative to IVIg in CIDP [Markvardsen *et al.* 2013; Lee *et al.* 2008; Bayas *et al.* 2013; Cocito *et al.* 2014]. One CIDP patient showed clinical fluctuation under SCIg therapy after 1 year and was treated successfully with adaptation of the dose (approximately 50% dose increase). This observation showed that mild clinical deterioration may be successfully treated with adaptation of the SCIg dose. In addition, the clinical stability achieved under subcutaneous therapy in a total of 5/6 patients shows that SCIg may be equally effective as IVIg.

It is noticeable that administration of SCIg seems to be highly effective in MMN patients. A favourable therapeutic response of MMN patients to SCIg therapy has already been reported in various studies [Eftimov *et al.* 2009; Misbah *et al.* 2011; Harbo *et al.* 2009, 2010]. The clinical stability of our MMN patient under SCIg dosages comparable with the IVIg maintenance dosage confirms previously reported findings from Eftimov and

colleagues [Eftimov *et al.* 2009]. On the other hand, reports on SCIg treatment in other neuromuscular disorders (MG and IBM) are rare. Pars and colleagues reported SCIg effects on dysphagia in IBM patients [Pars *et al.* 2013]. As far as we know reports of SCIg effects in treating MG are lacking. As both of our patients were treated with SCIg for more than 2 years, this is one of the first reports on long-term SCIg treatment in neuromuscular disorders to date. In both cases, clinical stability was achieved under SCIg dosages that were 30% (IBM) or 20% (MG) lower compared with the previous IVIg maintenance dosage.

Regarding the side effects, 4/6 patients in our study complained of mild side effects at the injection site, including redness, skin reaction and swelling, which were transient and of mild intensity. Noticeably, no systemic Ig side effects (e.g. headache, fever, hypertension, thromboembolic events) have been documented in our patients. Systemic adverse effects occur only in 7% of patients receiving Ig, while serious adverse effects may occur in 0.3% of patients [Debes *et al.* 2007]. Most side effects are thought to be due to the high peak levels of serum IgG produced by IVIg. In contrast, SCIg produces stable Ig concentrations leading to systemic adverse events in less than 1% of infusions with fever being the most frequent [Gardulf *et al.* 2006].

In general, SCIg was well tolerated by all patients in our study, showing that this therapy is feasible, practical and safe. Our findings are consistent with those of Harbo and colleagues showing that self-administration of SCIg has numerous advantages compared with IVIg [Harbo *et al.* 2010]. First of all, in view of the fact that an easily programmable pump is usually used to deliver SCIg, no venous access is required. The subcutaneous infusion technique is easy to learn and can be performed even by elderly patients at home. For most patients, self-administration results in improved convenience, better quality of life, avoidance of hospitalization, fewer side effects and improved flexibility. Therefore, all of our patients preferred the subcutaneous to the intravenous route of administration. On the other hand, the pharmacokinetics of Ig following intravenous and subcutaneous administration differ. Administration of IVIg leads to an immediate rise in serum Ig concentration to high levels, followed by a rapid fall over the following days. This decline is

associated not only with the passage of Ig from the vascular to the lymph and extracellular fluid compartments, but also by the catabolism of Ig [Misbah *et al.* 2011; Bonilla, 2008]. In contrast, the administration of SCIg is followed by slow diffusion into the vascular and extravascular fluid space [Bonilla, 2008]. Treatment with SCIg has an economic impact due to the reduction in hospitalization rate of patients when using SCIg [Högy *et al.* 2005; Gardulf, 2007; Berger, 2008], and the difference in price between the SCIg and IVIg preparations [Högy *et al.* 2005].

The limitations of our study include the retrospective character, the small study sample, including a heterogeneous group of patients, and the lack of quality-of-life measures. Although our data indicate the clinical efficacy of SCIg therapy in various autoimmune neuromuscular disorders, no sufficient conclusion could be drawn separately for each neuromuscular disorder. A long-term, prospective study of SCIg administration may provide more data on this aspect.

To conclude, SCIg can be an attractive alternative to IVIg treatment in various autoimmune neuromuscular disorders, such as CIDP, MMN, IBM and MG. The efficacy of SCIg, its rare systemic adverse effects, its adherence by patients and even preference over IVIg by patients is likely to be extendable to other autoimmune neuromuscular diseases.

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MSY acquired, analysed, interpreted the data and made the critical revision of this study. RG drafted the study design and made the critical revision of the data in this study. AK acquired, analysed and interpreted the data of this study.

Conflict of interest statement

MSY has received speaker honoraria from CSL Behring. RG has received consultation fees and speaker honoraria from CSL Behring, Bayer Schering, Biogen Idec, Merck Serono, Novartis, Sanofi and Teva. He also acknowledges grant support from Bayer Schering, Biogen Idec, Merck Serono, Sanofi and Teva, all unrelated to this manuscript. AK reports no disclosures.

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