Chronic inflammatory demyelinating polyneuropathy (CIDP), a chronic inflammatory disease of the peripheral nervous system (PNS), is clinically characterized by hypo- or areflexia and progressive or relapsing motor or sensory dysfunction developing over weeks. In the last two decades, clinical trials (class I evidence) have revealed the therapeutic efficacy of prednisolone, plasma exchange, and, in particular, intravenous immunoglobulins (IVIG), although these studies were focused on treatment of acute deteriorations. IVIG short-term therapy is based on clinical trials recommending the periodic administration of 0.4 g IVIG per kilogram body weight every 4 weeks. The immunomodulatory and anti-inflammatory actions of IVIG are complex and involve the modulation of expression and function of Fc receptors as well as an influence on complement activation and the cytokine network. Moreover, IVIG may contain anti-idiotypic antibodies and lead to an inhibition of maturation and altered function of dendritic cells as well as a modulation of T- and B-cell activation, differentiation and effector function.

The side effects of long-term steroid treatment, the high costs and shortage of IVIG, and the potential risks of plasma exchange as invasive therapy and the need for frequent hospitalizations underscore the need to develop innovative therapeutic regimens for the treatment of autoimmune diseases of the PNS. In genetic disorders such as primary (PID) and secondary antibody deficiencies, immunoglobulins have been administered for more than 25 years and have been proven to be safe, without long-term side effects. An alternative approach, the subcutaneous administration of immunoglobulins (SCIG) via a small portable pump, has been initiated for these disorders. This regimen is well established for children with PID and SCIG results in well-balanced IGG plasma levels while lowering peak concentrations in comparison to IVIG. Further data from these studies speak for reduced side effects and significant cost savings with SCIG. In particular, application of SCIG with a small portable pump at home can significantly improve quality of life by reducing the frequency of hospitalizations. Therefore, we explored the use of SCIG in CIDP in this preliminary, unblinded study.

Case Report: Patient 1
A 73-year-old woman had a 13-year history of definite CIDP confirmed by sural nerve biopsy and typical electrophysiological findings. Clinical examination at onset of disease revealed severely disturbed proprioception with gait ataxia. Motor nerve conduction velocities were between 35–37 m/s in the median nerve and sensory nerve action potentials were absent (Table 1).

Initially, treatment with corticosteroids led to an improved gait and corticosteroids were gradually tapered followed by clinical stabilization for six years. Nine years after disease onset she experienced a relapse with progressive sensory loss and mild to moderate distally pronounced tetraparesis requiring bilateral assistance for ambulation. Oral corticosteroids were resumed but resulted in long-term side effects (osteopenia and Cushing’s syndrome) and only temporary clinical benefit. Thus, therapy with intravenous cyclophosphamide pulses (600 mg/m2) was initiated.

Initially, treatment led to improvement of symptoms and the patient was able to walk without assistance. Due to severe side effects including diarrhea, hair loss, stomatitis, and hematologic changes, however, cyclophosphamide therapy had to be stopped after six cycles. Subsequently,
proprioception and tetraparesis deteriorated progressively and led to increasing impairment of mobility until the patient was chairbound. Two months after discontinuation of cyclophosphamide, therapy with IVIG was started and has continued for the last 18 months, with 60 g IVIG per month (two infusions of 30 g each, equaling 0.4 g/kg). Several attempts to lower IVIG dosing or to extend infusion intervals failed due to rapidly worsening tetraparesis three weeks later. Monthly IVIG administration led to a temporary, fluctuating stabilization. Central venous access was required to continue therapy. Meanwhile, additional immunosuppressive therapy with azathioprine had to be stopped after 17 months due to hepatotoxicity. Alternative immunosuppressive therapy with mycophenolate mofetil (1,500 mg per day) was well tolerated but did not stop progression of the disease and the patient was referred to our outpatient clinic for advice.

After obtaining informed consent, we initiated a treatment with SCIG following the previous IVIG regimen. To that end, a polyvalent immunoglobulin (Vivaglobin 160 mg/ml; Behring-Aventis, Marburg, Germany) and a portable, programmable pump (CRONO super PID; Mantsch-OMT, Minden, Germany) designed for a maximal syringe capacity of 20 ml were used. After being built-up gradually, the patient received a weekly SCIG dose of 16 g in a total volume of 100 ml infused over 10 h. The weekly dosage was divided into five equal doses administered over the course of three subsequent days, with each dosing containing 3.2 g SCIG in a volume of 20 ml (Fig. 1A). Due to subcutaneous swelling, the maximum dosage per day was limited to 6.4 g. Besides mild local skin reactions, treatment was well tolerated, without additional side effects. On therapy with SCIG for more than eight months, the patient has maintained her ability to walk with assistance (Table 1). Arm function also stabilized; hand-held vibrometer revealed stable grip strength of the right hand, with 30 kPa at the beginning of subcutaneous therapy and 30 kPa on day 138. This clinical stability was well reflected by the electrophysiological findings (Table 1).

**Table 1. Clinical and electrophysiological findings of patient 1 and patient 2 on treatment with SCIG.**

<table>
<thead>
<tr>
<th>Days after treatment</th>
<th>ISS</th>
<th>MRC</th>
<th>ODSS</th>
<th>CMAP (mV)</th>
<th>NCV (m/s)</th>
<th>DML (ms)</th>
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<tbody>
<tr>
<td><strong>Patient 1</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-183</td>
<td>5</td>
<td>20.5</td>
<td>7</td>
<td>3.1</td>
<td>42</td>
<td>5.6</td>
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<tr>
<td>-75</td>
<td>8</td>
<td>23.5</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>23.5</td>
<td>4</td>
<td>3.7</td>
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<tr>
<td>138</td>
<td>8</td>
<td>24.5</td>
<td>4</td>
<td>3.6</td>
<td>45</td>
<td>6.6</td>
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<tr>
<td>206</td>
<td>8</td>
<td>24</td>
<td>5</td>
<td>-</td>
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<tr>
<td><strong>Patient 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>-28</td>
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<td>4</td>
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<td>34.9</td>
<td>5.2</td>
</tr>
<tr>
<td>0</td>
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<td>5.1</td>
</tr>
</tbody>
</table>

Clinical measures include the sensory sum score\(^{10}\) for sensory deficits (ISS), the Medical Research Council sum score (MRC) for weakness,\(^{15}\) and the overall disability sum score\(^{15}\) to assess overall disability (ODSS). As a representative paraclinical measure, motor conduction studies of the right tibial nerve including assessment of amplitude of the compound muscle action potential (CMAP), nerve conduction velocity (NCV), and distal motor latency (ms) are shown. Day 0 indicates initiation of SCIG treatment; days preceded by a minus symbol indicate days prior to treatment.

**Case Study: Patient 2**

A 53-year-old man presented to another department with a five-year history of sensory symptoms; examination revealed impaired proprioception. A diagnosis of CIDP was established by typical findings in the cerebrospinal fluid with elevated total protein level and by a slowing of motor conduction velocities. Initiation of IVIG therapy (40 g/day over five days) led to complete remission of sensory symptoms. As maintenance therapy, immunosuppression with azathioprine was started. However, this regimen ➢
did not stop disease progression and his sensory symptoms worsened. Thus, treatment was switched to mycophenolate mofetil (1,500 mg per day), yet tingling, paresthesias, and atrophy of the distal leg and arm muscles developed. On examination at our outpatient clinic, he presented with moderate hypesthesia and paresthysesthesia in all four limbs as well as a distally pronounced, atrophic tetraparesis. At that time he was found to have slowed motor conduction velocities and compound muscle action potentials of decreased amplitude (Table 1). Informed consent was obtained and the patient was started on combination therapy with mycophenolate mofetil and SCIG. The dose of SCIG was built up gradually until he was receiving a weekly SCIG dose of 6.4 g in a total volume of 40 ml (FIG. 1B), all applied on one day (corresponding to a monthly SCIG dose of 25.6 g). Besides mild local skin swelling, side effects were not observed. On continued treatment for over two years, sensory as well as motor symptoms have remained clinically stable, a finding confirmed electrophysiologically. (Table 1)

**Figure 1.** Application scheme of SCIG for patient 1 (A) and patient 2 (B). Arrows indicate infusion of single SCIG doses each containing 3.2 g IG in a volume of 20 ml.

**Discussion**

The first experiences with subcutaneous administration via battery-powered syringe pumps were gained in the late 1970s, when Berger and colleagues introduced a pump for slow, subcutaneous administration of larger IG amounts. Since then, subcutaneous administration of IG has emerged as an alternative administration route both in children and adults for several indications and now should be considered for treatment of certain neuromuscular disorders.

The clinical efficacy of IVIG is well established in different inflammatory diseases of the PNS including multifocal motor neuropathy, Guillain–Barré syndrome, and CIDP. We have demonstrated a sustained effect of SCIG in CIDP in a 1:1 dose ratio compared to IVIG. The clinical stabilization of both of our patients suggests an equivalent efficacy of SCIG and IVIG. This observation is further corroborated by another case report describing effective treatment with SCIG in a patient with multifocal motor neuropathy.

Interestingly, the frequency of subcutaneous administration did not influence therapeutic efficacy in the present cases. Both patients remained clinically stable either with weekly pulses (patient 2) or more continuous application (patient 1). Although one study in panhypogammaglobulinemia reported inadequate efficacy of intramuscular IG compared to IVIG, further systematic data on application intervals, especially in neuromuscular diseases, are not available.

In the present cases both patients received mycophenolate mofetil as a concomitant immunosuppressive therapy. Several recent studies have suggested that mycophenolate mofetil monotherapy may be beneficial in patients with various neuromuscular disorders, including myasthenia gravis, myositis, and CIDP, and other reports have demonstrated the efficacy of combined treatment with mycophe-
nolate moefetil and IVIG. Further systematic clinical studies are needed to better define efficacy, combination therapy, optimal dosage, and application intervals of SCIG in neuromuscular diseases.

In our patients, SCIG treatment did not result in severe adverse effects. Apart from subcutaneous swelling, skin reactions or systemic side effects were not observed. In an observational study, 1,500 subcutaneous infusions were clinically followed: none of the patients displayed significant allergic reactions, thus confirming the tolerability of this approach. In patients with PID, SCIG was even reported to decrease systemic side effects compared to IVIG or intramuscular administration.

Further advantages of SCIG include increased patient autonomy and parental application without the need for venous access. The easy and independent handling of infusions reduced hospitalizations, especially in the first patient. Thus, treatment with SCIG contributes to maintenance of an independent life, and patients with PID report an improved quality of life. Limitations comprise a restricted volume that can be administered in one infusion, thus sometimes necessitating repetitive dosing to reach equivalence with intravenously applied dosages.

Finally, pharmacoeconomic aspects are important. In this regard, IVIG therapy represents a particularly costly regimen, sometimes limiting its clinical use. In the present cases, switching therapy from IVIG to SCIG reduced medication costs for immunoglobulin by 50% (e.g., in patient 1 from €60,000 to 30,000 using equivalent dosages). Thus, subcutaneous application may be not only safe and effective, but may reduce treatment costs in patients with chronic neuromuscular diseases.

We thank Dr. Moeller, Behring-Aventis Inc., and Mr. Meuser, Mantsch Inc., for their support in patient education of handling the programmable pump and self-administration of subcutaneous infusions.

References