Optimizing Chronic Inflammatory Demyelinating Polyneuropathy Care with Subcutaneous Immunoglobulin: The Polyneuropathy and Treatment with Hizentra Open-Label Extension (PATH OLE) Study and Beyond

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ABSTRACT

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a heterogeneous, acquired autoimmune neurological disorder affecting peripheral nerves. CIDP is characterized by progressive weakness, reduced or absent tendon reflexes and impaired sensory function in the lower and upper limbs. CIDP diagnosis is mainly based on clinical, laboratory and electrophysiologic criteria and there are currently no diagnostic or prognostic biomarkers. First-line treatment options include corticosteroids, intravenous immunoglobulin (IVIg) and plasma exchange (PLEX). While IVIg and corticosteroids are the most common therapies administered for CIDP, there are challenges associated with their use, including systemic adverse events (AEs), some of which can be serious. Studies have shown that subcutaneous immunoglobulin (SCIg) may be associated with improved quality of life, which is attributed partially to the patients' freedom to administer SCIg at home and at their convenience. While AEs with SCIg mostly consist of local site reactions, SCIg is associated with fewer systemic AEs compared with IVIg, and these are commonly mild, though severe reactions may rarely occur. A number of studies in the last decade have assessed SCIg in CIDP. One of these studies, the Polyneuropathy and Treatment with Hizentra® (PATH) study, was a global phase 3, double-blind, randomized, placebo-controlled trial that assessed the efficacy, safety, and tolerability of SCIg treatment in patients with CIDP. Based on the results of the PATH study, the US Food and Drug Administration (FDA) approved SCIg as a maintenance treatment for CIDP in 2018. This review summarizes and discusses the results of the PATH study and its open-label extension (OLE) study and provides an overview of the April 2021 update to the Hizentra® FDA-approved U.S. package insert based on findings from the PATH OLE. In addition, the review highlights key elements of the second revision of the European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) guideline for the diagnosis and treatment of CIDP. Finally, this review discusses the characteristics of patients with CIDP who may benefit from SCIg treatment.

Keywords: *Chronic inflammatory demyelinating polyneuropathy; Subcutaneous immunoglobulin; Immunoglobulin therapy; Maintenance therapy; Treatment guidelines.*

CIDP Pathophysiology

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune disorder that typically presents with symmetric distal and proximal weakness of the leg and arm muscles that progresses over more than 8 weeks, abnormal sensation such as tingling or numbness (beginning in the toes and fingers), and reduction or loss of deep tendon reflexes (hypo or areflexia) (1, 2). Additionally, less prominent symptoms of CIDP include fatigue, ataxia and neuropathic pain (1-3). The diagnostic criteria for CIDP were recently published (4), and a more detailed description of CIDP and its variants will follow in section '*Updated 2021 European Academy of Neurology (EAN)/ Peripheral Nerve Society (PNS) guideline*'.

The pathophysiology of CIDP is incompletely understood and involves mobilization of cellular and humoral autoimmunity, although the relative contribution of each is not well elucidated (1). CIDP is believed to be driven by heterogeneous immune-mediated processes (1). Humoral factors are thought to play a major role in CIDP pathogenesis, as demonstrated in passive transfer experiments using sera and purified IgG from patients with CIDP (5). The role of humoral factors in CIDP is also supported by the beneficial effects observed with plasma exchange (PLEX) while T cell activation leading to macrophage-induced myelin degradation supports the contribution of cellular immunity (6).

CIDP Epidemiology

Due to its heterogeneous presentation, CIDP diagnosis relies on findings from multiple modalities. CIDP is more common in males and can occur at any age, but the onset is usually between 40 and 60 years with peak prevalence in the 8th decade (4, 7).

An estimated 20–21% of neuropathy cases at large academic centers are inflammatory neuropathies (8, 9). A 2019 systematic review of 11 CIDP studies that reported the incidence and prevalence of CIDP, showed substantial heterogeneity between studies, which may partly be explained by the use of different diagnostic criteria (10). CIDP prevalence increased with age, and most patients were male, but no evident geographical variation in the incidence or prevalence rates was observed (10). The

reported prevalence of CIDP varies greatly, from 0.67 to 10.3 per 100,000 (10). In Olmsted County, Minnesota, at the start of 2000, CIDP had a prevalence of 8.9 per 100,000 (11). Between 1982 and 2001, CIDP incidence was 1.6 per 100,000 per year (11). A meta-analysis published in 2019 estimating the prevalence and incidence of CIDP worldwide, provided a pooled crude incidence rate for CIDP of 0.33 per 100,000 person-years and a pooled crude prevalence of 2.81 per 100,000 persons (10).

Current Treatments for CIDP

First line pharmacological treatments target immune dysfunction and include primarily induction with intravenous immunoglobulin (IVIg) or corticosteroids (e.g., prednisone) (4). PLEX (also known as plasmapheresis) is logistically complicated and is therefore recommended when IVIg and corticosteroids are ineffective (4). Choices for first line maintenance therapy include IVIg, subcutaneous immunoglobulin (SCIg), corticosteroids and possibly chronic PLEX (4). Immunosuppressive and immunomodulatory agents such as azathioprine, cyclophosphamide, rituximab, and mycophenolate mofetil are employed as second line therapeutic agents with limited evidence and variable results (4). Challenges with IVIg, corticosteroids and PLEX include systemic adverse events (AEs), some of which can be serious (12). A detailed description of the challenges associated with the aforementioned treatments is provided in a recent review (13). Retrospective cohort studies have reported that the incidence of thromboembolic events ranges from 10.6% to 16.9% in IVIg-treated inflammatory neuropathy patients (14-16). IVIg infusions also require monitoring by a clinician and can last four or more hours over one or several days (17). Regular peripheral venous access can be difficult to maintain for chronic intravenous (IV) treatments. Additionally, IVIg can be challenging to schedule for patients who work or travel (18). IVIg and SCIg exhibit comparable efficacy (19), but SCIg offers improved tolerability and enhanced autonomy and more stable IgG levels compared with IVIg (20).

IVIg infusions lead to a high post-infusion peak in serum IgG concentration at the end of the infusion, followed by a rapid decrease 48 hours post-infusion, and a slower decrease in IgG concentration over the next 30 days (21). This decline in IgG concentration can result in disease fluctuations and a return of symptoms prior to the next scheduled dose, also referred to as 'wear-off effects', which can be a concern as patients approach trough IgG values. Patients reporting wear-off effects may be suitable for considering dosage escalation (17). Wear-off effects are not typically seen with frequent SCIg administration, which is associated with stable, 'steady-state' plasma IgG levels between doses (22). Indeed, pharmacokinetic studies have shown that higher steady-state serum IgG levels are achieved with SCIg compared with IVIg, and that SCIg infusion results in higher trough and lower peak serum IgG levels than with IVIg, and smaller fluctuations in serum IgG levels (23, 24).

In the past decade, several studies have been conducted to investigate SCIg in CIDP. A meta-analysis evaluating results from eight of these studies, comprising 88 patients with CIDP and 50 patients with multifocal motor neuropathy, found that the use of SCIg was associated with a significant 28% reduction in the relative risk of moderate and/or systemic AEs compared with IVIg (20). In addition, studies have demonstrated an enhanced quality of life in patients with chronic inflammatory neuropathies receiving SCIg compared with IVIg therapy (25, 26).

The Polyneuropathy and Treatment with Hizentra (PATH) study (27), and its open-label extension (OLE) (28) demonstrated that SCIg is efficacious in maintaining patients previously stabilized on IVIg, and that treatment with SCIg beyond 24 weeks is safe and efficacious (**Table 1**). Both trials have been the catalyst for changes in treatment practices for the management of CIDP and improvement of patient care (27-29).

Hizentra®, a Subcutaneous Immunoglobulin

Hizentra®, Immune Globulin Subcutaneous (Human), 20% Liquid, is a ready-to-use, sterile 20% (0.2 g/mL) protein liquid preparation of polyvalent human immunoglobulin G (IgG) for subcutaneous (SC) administration. It is manufactured from large pools of human plasma through a combination of cold alcohol fractionation, octanoic acid fractionation, and anion exchange chromatography (29). In the U.S, Hizentra® is indicated for immunoglobulin replacement therapy in adult and pediatric patients with primary immunodeficiency (PID) (29-33), and for maintenance therapy in adults with CIDP to prevent relapse of neuromuscular disability and impairment (29).

As indicated in the US Prescribing Information (USPI), a limitation of use associated with SCIg treatment in CIDP is that Hizentra® maintenance therapy has been systematically studied for 6 months in the PATH study and for a further 12 months in the PATH OLE study (29). Maintenance therapy beyond these periods should be individualized according to the patient's response and need for continued therapy (29).

The safety profile of Hizentra® is similar to that of other SC IgG therapies in terms of the type, frequency, and treatment-relatedness of AEs (34, 35). Data from seven open-label, phase 3, prospective, multicenter studies of

Table 1. Summary of the PATH (27) and PATH OLE (28) studies

Study characteristic		PATH study	PATH open-label extension study
Study endpoints and key efficacy data	**Primary endpoint**	• Proportion of patients with a CIDP relapse or who were withdrawn for any other reason during 24 weeks of treatment o In the ITT set, 36 (63%) patients on placebo, 22 (39%) on 0.2 g/kg SCIg, and 19 (33%) on 0.4 g/kg SCIg had a relapse or were withdrawn from the study for other reasons (p=0.0007)	• Determine the long-term safety of SCIg (Hizentra®) in patients with CIDP o In all, 62 (76%) patients had AEs; most were mild (62%) or moderate (29%); 8 (10%) had severe AEs; 3 serious local reactions in 1 patient were causally related to SCIg with no related serious AEs; 7 (9%) patients had serious AEs none of which were causally related to SCIg
	Secondary endpoints	• Time to primary endpoint, INCAT score, I-RODS score, Grip strength (dominant hand), Grip strength (non-dominant hand), MRC sum score o The probability of reaching the primary endpoint was significantly lower in both SCIg groups compared with the placebo group (p=0.0005 [0.4 g/kg SCIg vs placebo] and p=0.007 [0.2 g/kg SCIg vs placebo]) o Changes from baseline: INCAT score, p<0.0001; I-RODS score, p=0.0002; Grip strength (dominant hand), p=0.02; Grip strength (non-dominant hand), p=0.003; MRC score, p=0.003	• Determine the long-term efficacy of SCIg (Hizentra®) in patients with CIDP o Overall relapse rates were 10% in the 0.4 g/kg group and 48% in the 0.2 g/kg group o Following dose reduction from 0.4 to 0.2 g/kg, 51% of patients relapsed, of whom 92% improved after re-initiation of the 0.4 g/kg dose o Two-thirds of patients (19/28) who completed the PATH study without relapse remained relapse-free on the low-dose following dose reduction in the extension study
Most frequently reported AEs		• Any AE: o 33 patients (58%) in the 0.2 g/kg SCIg group o 30 patients (52%) in the 0.4 g/kg SCIg group o 21 (37%) in the placebo group • General disorders and administration-site conditions: o 16 patients (28%) in the 0.2 g/kg SCIg group o 18 patients (31%) in the 0.4 g/kg SCIg group o 6 (11%) in the placebo group • Local reactions: o 11 patients (19%) in the 0.2 g/kg SCIg group o 17 patients (29%) in the 0.4 g/kg SCIg group o 4 (7%) in the placebo group	• Any AE: o 33 patients (45%) in the 0.2 g/kg SCIg group o 46 patients (64%) in the 0.4 g/kg SCIg group • General disorders and administration-site conditions: o 8 patients (11%) in the 0.2 g/kg SCIg group o 18 patients (25%) in the 0.4 g/kg SCIg group • Local reactions: o 7 patients (10%) in the 0.2 g/kg SCIg group o 13 patients (18%) in the 0.4 g/kg SCIg group
Patient preference		Preferred current treatment: • 61 (53%) of 115 patients who received SCIg o 30 (53%) in the 0.2 g/kg group o 31 (53%) in the 0.4 g/kg group • 22 (39%) of 57 patients who received placebo Preferred previous IVIg treatment: • 21 (18%) patients receiving SCIg • 10 (18%) and 11 (19%) and 14 (25%) patients receiving placebo	Preferred current treatment: • 61 (82%) of patients preferred their current SC treatment o 35 (90%) in the 0.2 g/kg group o 50 (83%) in the 0.4 g/kg group Preferred previous IVIg treatment: • 9 (12%) of patients preferred their previous IVIg treatment o 2 (5%) in the 0.2 g/kg group o 7 (12%) in the 0.4 g/kg group

Abbreviations: AE, adverse event; CIDP, chronic inflammatory demyelinating polyneuropathy; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Neuropathy-Rasch-Built Overall Disability Scale; ITT, intention-to-treat; IVIg, intravenous immunoglobulin; MRC, Medical Research Council; PATH, Polyneuropathy and Treatment with Hizentra; SC, subcutaneous; SCIg, subcutaneous immunoglobulin

the efficacy and safety of Hizentra®, conducted in Japan, Europe, and the U.S showed that Hizentra® is well tolerated; reported AEs were predominantly mild or moderate, and mostly consisted of local injection-site reactions (ISRs) (36).

Optimizing CIDP Care with SCIg: The PATH Study

The PATH study was a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group 3-arm study that evaluated the efficacy and safety of two doses of Hizentra® (0.2 g/kg body weight or 0.4 g/kg body weight) versus placebo during a 24-week SC treatment period in patients with CIDP who had previously responded to IVIg treatment (**Table 1, Figure 1A**) (27).

Following screening, all eligible patients progressed through three study periods: an IgG dependency test period (lasting up to 12 weeks), a period of restabilization on IVIg (lasting up to 13 weeks), and a randomized SC treatment period (24 weeks of treatment with a final assessment at Week 25) (27). The IgG dependency test period was necessary to ensure that only patients who were still in need of IgG were randomly allocated (27). Only those patients who were established to be IgG dependent were enrolled in the IVIg restabilization period.

During the SC treatment period, a total of 172 patients were randomly allocated to three groups: 57 (33%) to the placebo group, 57 (33%) to the 0.2 g/kg SCIg group, and 58 (34%) to the 0.4 g/kg SCIg group (27). The primary outcome was the proportion of patients with a CIDP relapse or who were withdrawn for any other reason during the 24 weeks of treatment (27). A CIDP relapse was defined as a deterioration (i.e., increase) by at least 1 point in the adjusted (by excluding a 0 to 1 change in the arm score) Inflammatory Neuropathy Cause and Treatment (INCAT) disability score (range 0 [healthy] to 10 [unable to make any purposeful movements with arms and wheelchair-bound]) (37) at any SC treatment period visit compared with baseline (baseline scores were defined as the scores assessed at the end of the IVIg restabilization period) (27).

Secondary outcomes for the SC treatment period were time to the primary endpoint, INCAT score, mean grip strength for both hands separately, Medical Research Council sum score (range 0–80; including shoulder abduction, elbow flexion, wrist extension, index finger abduction, hip flexion, knee extension, foot dorsiflexion, and great toe dorsiflexion), and Inflammatory Neuropathy-Rasch-Built Overall Disability Scale (I-RODS; range 0 [most severe activity and social participation limitations] to 100 [no activity and social participation limitations]) (27).

The proportion of subjects experiencing a CIDP relapse or those who were withdrawn for any other reason (the primary endpoint) significantly favoured both SCIg groups as compared to the placebo group (p=0.007 [0.2 g/kg SCIg vs. placebo] and p=0.0005 [0.4 g/kg SCIg vs. placebo]) (27). In the intention-to-treat set, 36 (63%) patients on placebo, 22 (39%) patients on 0.2 g/kg SCIg, and 19 (33%) patients on 0.4 g/kg SCIg relapsed or were withdrawn from the study for other reasons (p=0.0007) (27). The absolute relapse risk reduction was 25% in the 0.2 g/kg SCIg group (p=0.007) and 30% in the 0.4 g/kg SCIg group (p=0.001) compared with placebo (27). The potential to prevent relapse with SCIg in PATH was overall similar to that documented for IVIg in previous studies, though there are no head-to-head comparisons (37). This randomized trial in patients with CIDP is the largest to date and the only to study two doses of SCIg in parallel (27). Based on the PATH study results, the FDA approved Hizentra® as a maintenance therapy for CIDP in March 2018 (29).

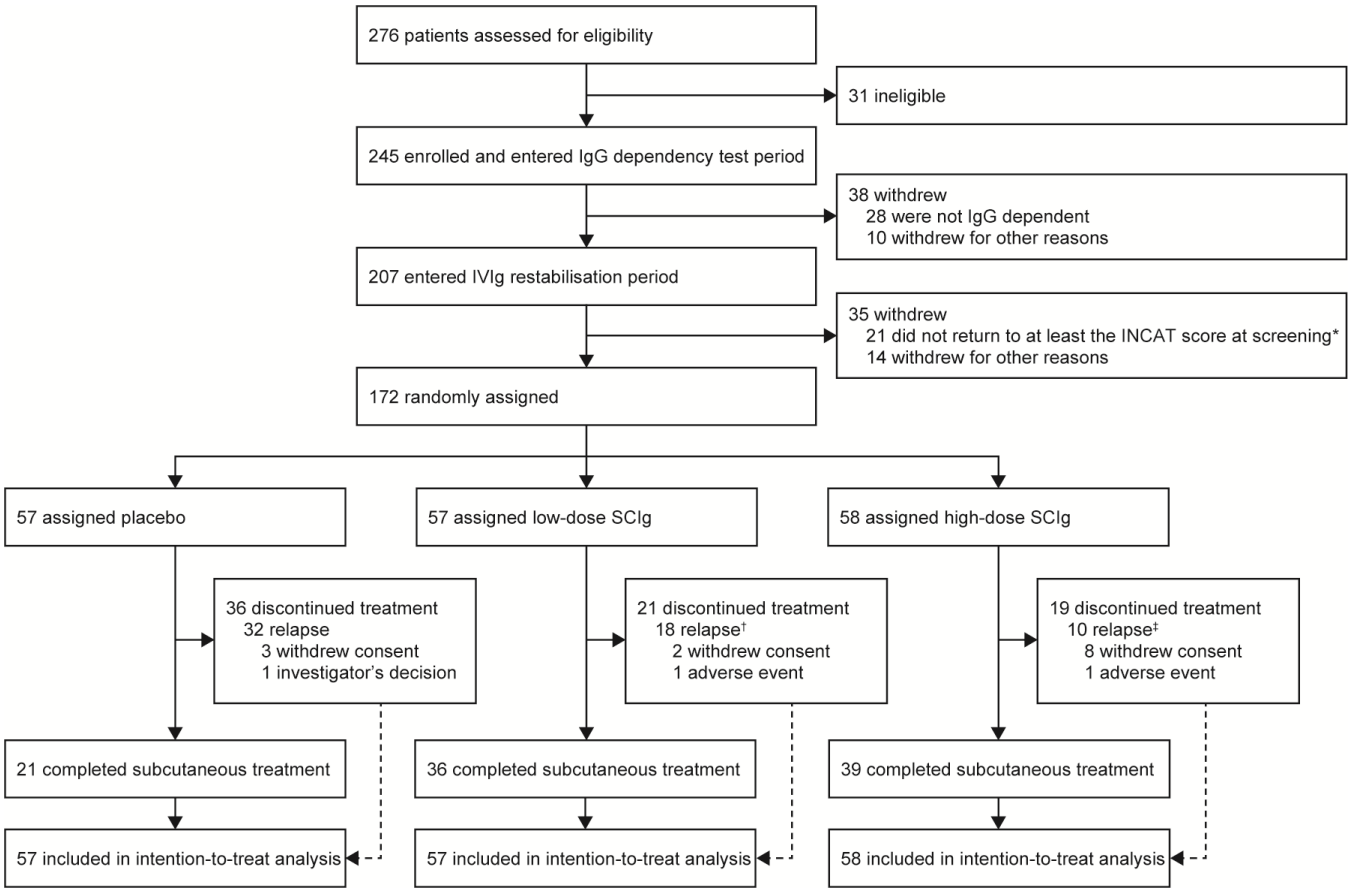
The findings from the PATH study have practical implications for the treatment of CIDP, demonstrating that patients on a standard regimen of IVIg can be safely transitioned to SCIg. The recently updated EAN/PNS treatment guideline recommend individualization of IgG dose, by using the same mean dose (1:1) per week when switching patients with CIDP from IVIg to SCIg. If the treatment effect is found to be insufficient, the guideline recommends that the dose be adjusted using reliable outcome measures (4). In line with the updated EAN/PNS treatment guideline, it is good practice to tailor SCIg doses in the range between 0.2–0.4 g/kg, based on patient intrinsic factors: previous IVIg dose and frequency, overall social situation and clinical response (4, 27, 29).

Optimizing CIDP Care with SCIg: The PATH Open-label Extension Study

This 48-week prospective open-label extension to the PATH study aimed to investigate the long-term safety and efficacy of weekly SC Hizentra® in CIDP (**Table 1, Figure 1B**) (28). In total, 82 patients were enrolled; 62 patients initially received 0.4 g/kg weekly, and 20 patients received 0.2 g/kg weekly. Clinically stable patients switched to 0.2 g/kg weekly after 24 weeks (28). After a protocol amendment, the low dose (0.2 g/kg weekly) was chosen as the initial dose. Patients remained on the 0.2 g/kg dose for 48 weeks unless relapse occurred, in which case the patients were given the option to switch to 0.4 g/kg. CIDP relapse was defined as a deterioration by at least 1 point in the total adjusted INCAT score (28).

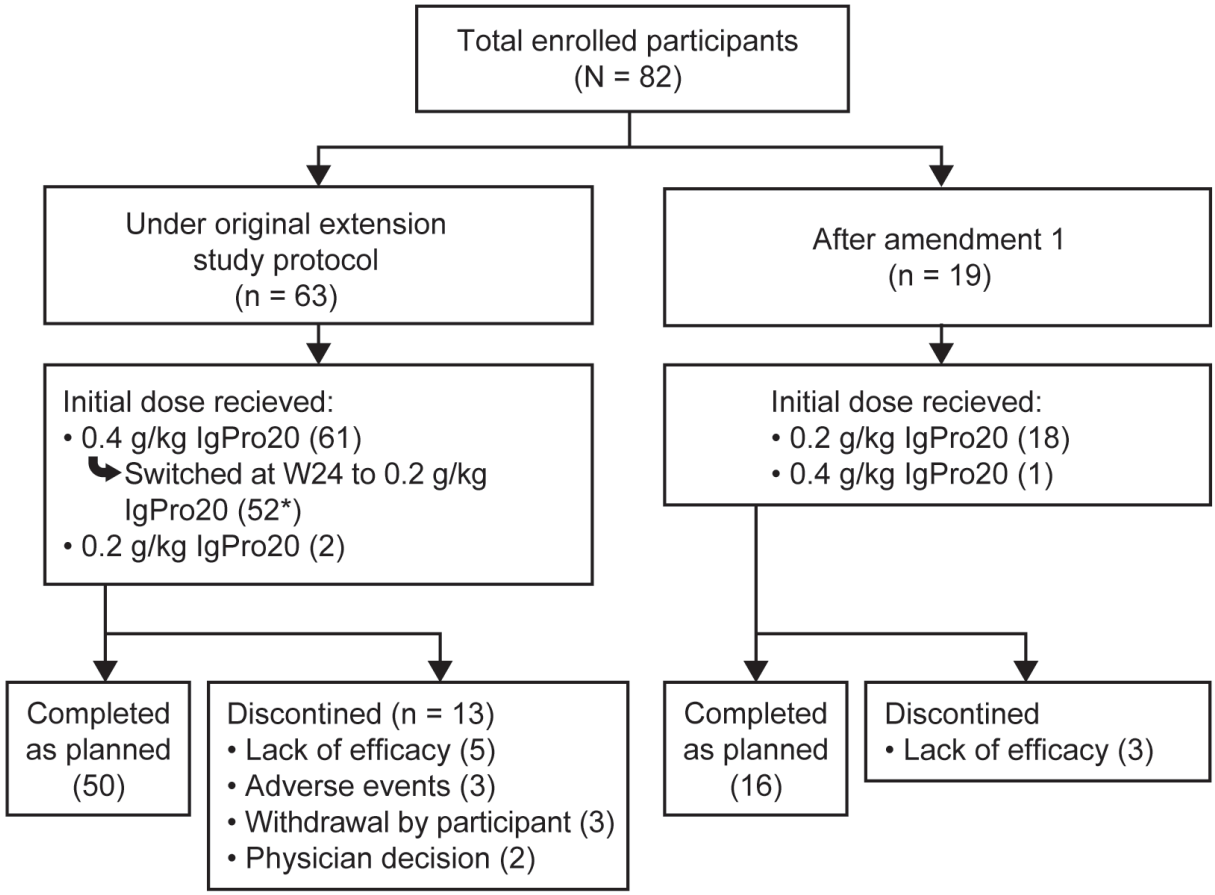
Of the 62 patients who initially received 0.4 g/kg SCIg, 52 switched to 0.2 g/kg SCIg after 24 weeks, of whom 26 (50%) relapsed (28). Overall relapse rates were 48% in patients treated with 0.2 g/kg SCIg, and 10% in patients

Figure 1. Trial design for PATH and PATH-OLE studies
A. PATH study design (Diagram taken from van Schaik IN et al. 2017 (27))



Abbreviations: INCAT, Inflammatory Neuropathy Cause and Treatment; PATH, Polyneuropathy and Treatment with Hizentra; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin
Footnotes: *An additional patient did not return to at least the INCAT score at screening, but was randomly allocated in error. †One patient relapsed at the end of study visit, but was not discontinued, so the total number of patients with a relapse in the low-dose group was 19. ‡One patient relapsed at the end of study visit, but discontinued the study because of an adverse event, so the total number of patients with a relapse in the high-dose group was 11.

B. PATH-OLE study design (Diagram taken from van Schaik IN et al. 2019 (28))



Abbreviations: PATH-OLE, Polyneuropathy and Treatment with Hizentra open-label extension
Footnotes: *Including one subject who relapsed twice on high dose but switched to low dose at week 24 and discontinued due to lack of efficacy.

treated with 0.4 g/kg SCIg (28). Of the 35 patients who relapsed on 0.2 g/kg SCIg, 31 (89%) improved within 4 weeks after re-initiation of 0.4 g/kg SCIg (28). Three of the 7 relapses (43%) occurring on 0.4 g/kg SCIg improved spontaneously without further intervention. Two-thirds of patients (19/28) who completed the PATH study without a relapse remained relapse-free after switching from 0.4 g/kg SCIg to 0.2 g/kg SCIg in the OLE (28). Overall, AEs were reported in 62 patients (76%), of which most were mild or moderate (28). Seven patients (9%) had 8 serious AEs (SAEs); none of these events were considered causally related to SCIg. Twelve severe AEs were reported in 8 patients (10%). All severe AEs resolved, except for a pre-existing vitamin D deficiency in 1 patient in the low-dose group, and 1 AE of infusion site swelling and 1 AE of infusion site erythema, which occurred in the same patient in the 0.4 g/kg SCIg group. Two patients were discontinued from the study as a result of AEs while on 0.2 g/kg SCIg and 1 patient while on 0.4 g/kg SCIg (28).

At study end, 82.4% of patients preferred their current SC treatment (28). In comparison, 12.2% of patients preferred IV treatment, whereas 5.4% had no preference on the route of administration. Most patients (71.6%) preferred SCIg treatment as the treatment was believed to offer more independence (28). The second most common reason (as reported by 40.5% of patients) for SC preference was spending less time receiving therapy (28). Other reasons for SCIg preference included "preferred frequency of administration", "my therapy works better" and "seem to feel fewer side effects", reported by 37.8%, 35.1% and 31.1% of patients, respectively (28).

The PATH OLE study demonstrated that SC treatment with Hizentra® provides prolonged benefit at both 0.2 g/kg and 0.4 g/kg weekly doses and suggested lower relapse rates on the higher dose (28). Importantly, a substantial proportion of patients can be switched from 0.4 to 0.2 g/kg weekly SCIg dose without further worsening, emphasizing that in clinical practice, dose reductions should be

considered in optimally treated and stable patients, and patients who relapse can be treated by increasing the dose of SCIg (28).

Updated Hizentra® U.S Food and Drug Administration (FDA) US Prescribing Information: April 2021

The previous FDA prescribing information for Hizentra® in the treatment of CIDP required that if patients worsened while receiving 0.2 g/kg body weight per week SCIg, then IVIg should be re-initiated. In April 2021 the prescribing information was updated to no longer require stabilization with IVIg if a patient worsens while on 0.2 g/kg weekly SCIg. The FDA-approved update now recommends that if CIDP symptoms worsen while receiving 0.2 g/kg SCIg, an increase to 0.4 g/kg per week should be considered (29).

The update to the USPI includes the results of the PATH OLE study, which demonstrated that after transitioning from IVIg to SCIg, both SCIg doses (0.2 g/kg or 0.4 g/kg) were effective in preventing CIDP relapse, with the 0.4 g/kg dose more likely to prevent relapse (27, 29). In cases where CIDP symptoms worsen on 0.4 g/kg, re-initiating therapy with IVIg, while discontinuing Hizentra®, should be considered. Additionally, it is important to monitor patients' clinical response and adjust duration of therapy based on the individual needs of the patient (29).

Updated 2021 European Academy of Neurology (EAN)/ Peripheral Nerve Society (PNS) guidelines

The 2010 consensus guideline on CIDP (38) has been revised, and the clinical criteria for defining CIDP into 'typical CIDP' and 'CIDP variants' have been refined in the updated 2021 EAN/PNS guidelines on the diagnosis and treatment of CIDP (4). A description of the clinical characteristics of typical CIDP and CIDP variants is provided in **Table 2.** The aim of the update was to optimize diagnostic accuracy and to improve patient outcomes. The updated guideline provides more clarity on the clinical definition, electrophysiologic criteria, implications of nodal and paranodal antibodies, and individualization of treatment for CIDP. Among the notable changes, the previous term 'atypical CIDP' is no longer used and has been replaced by 'CIDP variants'. SCIg was strongly recommended as maintenance treatment in IVIg-responsive patients with active disease. While anti-myelin associated glycoprotein (MAG) neuropathy was not previously considered as part of CIDP, autoimmune nodopathies and chronic immune sensory polyradiculopathy are no longer considered subtypes or variants of CIDP (4).

Diagnostic criteria

Specific electrodiagnostic and clinical criteria were described, which are used to support the clinical diagnosis of typical CIDP and CIDP variants (**Table 2**) (4).

A comparison of the 2010 and 2021 electrodiagnostic criteria for a CIDP diagnosis is provided in **Table 3**. The revised EAN/PNS guideline has updated the motor nerve conduction criteria in support of the clinical diagnosis of CIDP (4). The distal compound muscle action potential (CMAP) duration increase (measured as the interval between onset of the first negative peak and return to baseline of the last negative peak) for support of the clinical diagnosis of CIDP in the 2010 guidelines was defined as median ≥ 6.6 ms, ulnar ≥6.7 ms, peroneal ≥ 7.6 ms, and tibial ≥ 8.8 ms (38). In the 2021 guideline, for distal CMAP duration prolongation, separate criteria were defined for four different low frequency filter (LFF) settings of 2, 5, 10, and 20 Hz (4). These criteria have been summarized in **Table 4**.

In patients fulfilling the clinical criteria for typical CIDP but not the electrodiagnostic criteria, the diagnosis of possible typical CIDP may be made if there is objective improvement with IVIg, plasma exchange, or corticosteroids, and if at least one additional supportive criterion (imaging [ultrasound, documenting nerve swelling at the site of conduction block], cerebrospinal fluid [CSF], or nerve biopsy) is met (4).

Clinical presentations different from typical CIDP are now considered CIDP variants, and not 'atypical CIDP'. The EAN/PNS 2021 guideline defines five CIDP variants: distal CIDP, multifocal CIDP, focal CIDP, sensory CIDP, and motor CIDP; however, no biomarkers specific to each clinical subtype have been identified (4, 39). A detailed description of the electrodiagnostic criteria for typical CIDP and CIDP variants is provided in **Table 2**.

Differential diagnosis

Aside from a combination of clinical, electrodiagnostic and laboratory features, the diagnosis of CIDP relies on exclusion of other disorders that may mimic CIDP (4). Differential diagnoses include drug or toxin exposure, IgM monoclonal gammopathy, elevated titer of antibodies to MAG, as well as other causes for a demyelinating neuropathy such as POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) and osteosclerotic myeloma (4).

Autoimmune nodopathies

Antibodies against nodal and paranodal cell-adhesion molecules (contactin-1 [CNTN1], neurofascin-155

Table 2. Clinical characteristics and electrodiagnostic criteria for typical CIDP and CIDP variants (4)

Typical CIDP and CIDP variants	Clinical description	Electrodiagnostic criteria
Typical CIDP	• Characterized by Progressive symmetric proximal and distal muscle weakness, decreased or absent deep tendon reflexes and sensory loss • The clinical course is most commonly progressive over more than 8 weeks • In up to 13% of CIDP cases, the clinical onset is acute, but patients continue to deteriorate for more than 8 weeks after onset or relapse at least three times after initial improvement with therapy, also known as the relapsing-remitting form	• To confirm the clinical diagnosis of typical CIDP, at least two motor nerves must have abnormalities which fulfil the motor conduction criteria • If criteria are fulfilled in only one nerve, the diagnosis is possible typical CIDP • Sensory conduction abnormalities must be present in at least two nerves to confirm the clinical diagnosis of typical CIDP
Distal CIDP	• Weakness in distal CIDP predominantly affects distal legs with distal arm and leg sensory loss leading to ataxia of gait • Those with IgM monoclonal gammopathy and those with nodal/paranodal antibodies are excluded from the distal CIDP category	• Motor conduction criteria fulfilment is required in at least two upper limb nerves to confirm the clinical diagnosis of distal CIDP • The distal CMAP amplitude should be at least 1 mV • If the motor conduction criteria are fulfilled in only 1 arm nerve or only in 2 leg nerves, the diagnostic certainty is possible distal CIDP • Sensory conduction abnormalities must be present in at least two nerves
Multifocal CIDP	• Also known as Lewis-Sumner syndrome or MADSAM • Usually affects the upper limbs first; lower limbs may be involved, but this occurs later on in the disease course	• Motor conduction criteria fulfilment is required in at least two nerves in total in more than one limb to confirm the clinical diagnosis of multifocal CIDP • Sensory conduction abnormalities must be present in at least two nerves of the affected limbs for the diagnosis of multifocal CIDP
Focal CIDP	• Focal CIDP is rare and typically affects the brachial or lumbosacral plexus, but can also affect individual peripheral nerves	• Motor conduction criteria fulfilment is required in at least two nerves in one limb for the diagnosis of focal CIDP • Sensory conduction abnormalities must be present in at least two nerves of the affected limbs for the diagnosis of focal CIDP
Sensory CIDP	• Sensory CIDP is characterized by sensory symptoms and signs (gait ataxia, impaired vibration and position sense, and changes in cutaneous sensation) without motor involvement	• A sensory CIDP diagnosis must fulfil sensory conduction criteria while motor conduction must be normal in all of at least four nerves • Sensory CIDP is often a transient clinical stage that precedes the appearance of weakness in about 70% of patients. Therefore, the maximum diagnostic certainty is possible sensory CIDP
Motor CIDP	• Patients with motor CIDP present with relatively symmetric progressive proximal and distal weakness with normal sensation clinically and electrophysiologically	• Motor CIDP diagnosis must fulfil motor conduction criteria in at least two nerves and sensory conduction must be normal in all of at least four nerves

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; CMAP, compound muscle action potential; IgM, immunoglobulin M

Table 3. A comparison of the EAN/PNS 2021 (4) and EFNS/PNS 2010 (38) electrodiagnostic criteria for the diagnosis of CIDP

NCS Parameter	EAN/PNS 2021 Definite CIDP One out of 8 NCS parameters each in two nerves	EFNS/PNS 2010 Definite CIDP One out of 8 NCS parameters each in two nerves
NCV	≥30%	≥30%
F-wave	≥20% or 50%*	≥30 or 50%*
DML	≥50%**	≥50%**
F-wave‡	Absent † + **1**	Absent † + **1**
CB	≥30% † (not tibial)	≥50% †
CB‡	In 1 nerve † + **1** (not absent F)	In 1 nerve † + **1**
TD	>30% (except tibial 100%)	>30%
Distal CMAP duration‡	In ≥1 nerve + **1**	In ≥1 nerve + **1**

Abbreviations: CB, conduction block; CIDP, chronic inflammatory demyelinating polyneuropathy; CMAP, compound muscle action potential; DML, distal motor latency; EFNS, European Federation of the Neurological Societies; EAN, European Academy of Neurology; LLN, lower limit of normal values; NCS, nerve conduction study; NCV, nerve conduction velocity; PNS, Peripheral Nerve Society; TD, temporal dispersion
Footnotes: *cut-off values depend on CMAP amplitude being < or ≥80% LLN.
** Excludes median nerve at the wrist.
† CMAP amplitude must be ≥20% LLN.
‡ This abnormal NCS parameter can be present in only 1 nerve but is associated with another NCS abnormality in a different nerve. It is referred to in the table as +1.

Table 4. Summary of distal CMAP duration prolongation criteria for the clinical diagnosis of CIDP, according to the revised EAN/PNS guideline (4)

LFF setting (Hz)	Distal CMAP duration (ms)			
	Median nerve	Ulnar nerve	Peroneal nerve	Tibial nerve
2	> 8.4	> 9.6	> 8.8	> 9.2
5	> 8.0	> 8.6	> 8.5	> 8.3
10	> 7.8	> 8.5	> 8.3	> 8.2
20	> 7.4	> 7.8	> 8.1	> 8.0

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; CMAP, compound muscle action potential; EAN, European Academy of Neurology; LFF, low frequency filters; PNS, Peripheral Nerve Society

[NF155], contactin-associated protein 1 [Caspr1], and neurofascin isoforms NF140/186) have been detected in a small subset of patients fulfilling 2010 EFNS/PNS criteria for CIDP. More recent studies reported a higher frequency of autoantibodies against these proteins (up to 12% of patients diagnosed with CIDP) (4, 39). The presence of autoantibodies against the nodal-paranodal cell-adhesion molecules (CNTN1, NF155, Caspr1, and NF140/186) is now associated with conditions known as 'autoimmune nodopathies', which were previously regarded as CIDP variants (4). A study conducted by Querol and colleagues reported that antibodies against yet-to-be-identified antigens are detectable in a larger proportion of patients with CIDP (39). In IgG immunocytochemistry experiments, 24.6% of patients showed reactivity against dorsal root ganglion neurons, 12.3% showed reactivity

against Schwann cells, and 5.3% showed reactivity against motor neurons (39).

The updated EAN/PNS guideline now considers autoimmune nodopathies a separate entity from CIDP, because they lack classical hallmarks of CIDP, including overt inflammation and macrophage-mediated demyelination, and are poorly responsive or refractory to IVIg (4). The updated guideline also suggests considering testing for nodal and paranodal antibodies in all patients with clinical suspicion of CIDP, to rule out autoimmune nodopathies (4).

Antibodies against CNTN1 are associated with acute or subacute disease onset and motor or ataxic features (4). Antibodies against NF155 were detected in patients diagnosed with CIDP who were younger at onset and had a subacute or chronic disease course, distal weakness, ataxia and tremor (4). Evidence suggests paranodal NF155 and CNTN1 are the most consistent and clinically relevant targets and demonstrate a pathogenic role in immune neuropathies (40, 41). Antibodies against Caspr1 are linked to an acute/subacute neuropathy frequently associated with ataxia, neuropathic pain and cranial nerve involvement (4).

Treatment of CIDP

The updated EAN/PNS guideline strongly recommends first line treatment with IVIg, corticosteroids or PLEX (4). Although there is only very low certainty evidence, the guideline advises for the use of second line therapy with azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, and rituximab (4). Second line therapies are to be employed after failure of proven effective first line therapy or as add-on medication to reduce dosage or optimize therapeutic response of first line therapies (4).

The new guideline recommends the use of SCIg for maintenance treatment in CIDP, but either IVIg or SCIg can be used for maintenance treatment (4). During follow-up, dosage should be adjusted according to individual treatment response. Data suggest that there is insufficient evidence that 0.4 g/kg weekly is more efficacious than 0.2 g/kg weekly for maintenance treatment, but the PATH OLE reported lower relapse rates in patients receiving the 0.4 g/kg dose (4, 28). Limited available evidence indicates that patients with CIDP might in some cases require higher mean doses of SCIg compared with their previous IVIg dose. Additionally, the updated guideline recommended weakly against using SCIg for induction treatment in CIDP due to lack of evidence, as currently there has been only one small cross-over trial involving 20 patients, which reported earlier maximal improvement in motor performance following IVIg treatment, as compared with SCIg treatment (42).

The guideline revision recommended that the same mean dose (1:1) per week is a reasonable starting point, when patients with CIDP switch from IVIg to SCIg (4). If the treatment is insufficient, the dose should be adjusted based on reliable outcome measures. If the dose is high (>20–30 g/infusion), an option is to split doses, increase frequency of infusions or use multiple injection sites for SC infusions (4). Patient personal preference should be considered when making decisions regarding the use of SCIg or IVIg (4). Advantages associated with the use SCIg include autonomy and convenience of self-administration at home, avoiding IV cannulation, and possibly reduced frequency of systemic AEs (18, 20, 26). Additionally, with IVIg objective end-of-dose low IgG serum concentrations before the next IVIg infusion may occur (4). If this happens, the guideline recommends minimising this effect by increasing the IVIg dose or shortening the infusion interval (4). Disadvantages associated with the use of SCIg include local side effects (infusion site swelling and pain) and the need for more frequent infusions (4).

Beyond the EAN/PNS 2021 guidance – when should clinicians consider conversion from IVIg to SCIg

It is this author's opinion that other patients with CIDP could also be considered as candidates for conversion from IVIg to SCIg. A recently published review by Goyal et al provides detailed guidance for clinicians including when to consider SCIg, and when to initiate the transition from IVIg to SCIg (43). Patients who are likely to benefit from a switch to SCIg are those with venous access problems and those who have been previously affected by IVIg-related adverse effects, in particular headaches and nausea (44).

SCIg administration is associated with stable serum IgG levels (45). SCIg treatment can be self-administered at home, allowing for more flexibility, convenience and autonomy (18). Logistically, SCIg is less complicated than IVIg, and does not require hospital visits (34). During the coronavirus disease 2019 (COVID-19) pandemic, a switch from IVIg to SCIg in stable patients with CIDP has the potential to reduce nursing resource utilization, which are already stretched to the limit. Self-administration at home was encouraged during the COVID-19 pandemic, as it allowed patients to continue their treatment outside hospitals and minimized the risk of SARS-CoV-2 infection (46). Fewer hospital resources and reduced nursing capacity also contributed to patients switching from IVIg to SCIg. A study conducted in Canada demonstrated that a transition from IVIg to less labor-intensive SCIg had the potential to alleviate nurse shortages and decrease overall health care costs (47).

Conclusion

This review discussed recent advancements in treatment strategies in CIDP and the updated EAN/PNS CIDP guideline (4, 29). Through a discussion of the PATH studies, the updates to the Hizentra® FDA prescribing information of April 2021, and the 2nd revision of the EAN/PNS guideline for the diagnosis and treatment of CIDP, this review explored the evolution and role of SCIg in optimizing CIDP care and management (4, 27-29).

The PATH and PATH open-label extension studies provide evidence for the efficacy of SCIg as a maintenance therapy in CIDP (27, 28). Results from these studies were included in an update to the U.S prescribing information for Hizentra® in April 2021 (29).

The 2021 EAN/PNS guideline outlined a comprehensive approach to the management of CIDP (4). The revised guideline provided an updated clinical definition and supportive electrophysiologic criteria for the diagnosis of CIDP (4). Autoimmune nodopathies were listed as a separate entity from CIDP; their diagnosis has been associated with the presence of nodal and paranodal antibodies (4). Recommendations for individualized treatment and the use of SCIg were also included in the revised guideline (4).

CIDP is a clinically heterogeneous disease with complex pathophysiology and diagnosis, and relatively few treatment options. Despite these challenges, significant advancements have been made to understand the pathogenesis, simplify the diagnosis and provide better treatment for patients. Results from the PATH studies demonstrated that SCIg provided patients with an alternative to IVIg, offering improved tolerability as well as convenience and independence (27, 28). Ongoing and future clinical trials may provide further insights into treatment strategies for CIDP.

Competing interests

Dr. Dimachkie serves or recently served as a consultant for Amazentis, ArgenX, Catalyst, Cello, Covance/Labcorp, CSL-Behring, EcoR1, Janssen, Kezar, Momenta, NuFactor, Octapharma, RaPharma/UCB, Roivant Sciences Inc, RMS Medical, Sanofi Genzyme, Shire Takeda, Scholar Rock, Spark Therapeutics, Third Rock and UCB Biopharma.

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