Patient-reported Outcomes—An Emerging Cornerstone of Effective Intravenous Immunoglobulin Therapy

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Abstract

Intravenous immunoglobulin (IVIG) therapy is increasingly important in the management of various immune-mediated neuromuscular disorders including chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), myasthenia gravis (MG), and other neuromuscular disorders. Administrative burden, quality of life (QoL) concerns, adverse event prevention, economic pressures, and logistical factors are driving greater IVIG use into the home setting where it is administered by nurses. Patient-reported outcome measures (PROMs) are self-assessment instruments designed to measure a patient's disability, QoL, or their perceptions of health status in relation to specific diseases. PROMs may be a valuable means of monitoring disease status and treatment efficacy in patients receiving IVIG at home. Case reports and small clinical studies show that various specific and general purpose PROMs, such as the 15-item MG-specific QOL (MG-QOL15) and the Myasthenia Gravis Activities of Daily Living scale (MG-ADL), can provide valuable information for patient monitoring at home. PROMs may help to alert physicians that earlier follow-up or treatment regimen changes are needed. PROM data recording systems such as Walgreens' PartnerPoint Clinical Management℠ maintain regular reporting to the physician and enable efficacy and adverse events to be tracked. Pilot studies of patients with neuromuscular disease receiving IVIG at home demonstrate a strong correlation in PROM scores between assessments administered by pharmacy clinical staff and those administered by physicians indicating the reliability and suitability of PROMs for remote patient management. Further work to validate additional commonly used PROMS for autoimmune disease is needed if they are to be useful when administered outside the physician clinic.

Keywords

Patient-reported outcome measures, IVIG therapy, neuromuscular disease, improving care continuum

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Patient-reported Outcome Measures

The primary aim of treating disease is to give patients freedom from symptoms, disability and side effects, and the freedom to function. Objectively and reliably measuring disability and quality of life (QoL) can be challenging but using patient-reported outcome measures (PROMs), in addition to clinical examination by physician, has proved a valuable means of capturing patient status and response to treatment.[1–3] In disease management, PROMS can be used to estimate symptoms (severity/tolerability of dysfunction or symptom), function, and health-related QoL [HRQoL], such as psychologic well-being, social, and physical functioning). The US Food and Drug Administration (FDA) encourages validated PROMs as parameters that can support labeling requirements. They can be used as endpoints in clinical studies and in regular clinical use.[4] The FDA industry guidelines support the use of outcomes measures for specific neuromuscular disorders such as use of the Rasch-built Overall Disability Scale (R-ODS) in the management of chronic inflammatory demyelinating polyneuropathy (CIDP).[5]

Case Example 1

A 70-year-old male with a 25-year history of MMN showed right ulnar neuropathy at onset and subsequently showed left foot drop, right radial, and upper trunk symptoms with episodes occurring every 6–8 months at which time a course of 1 g/kg IVIG was prescribed. Following IVIG, he reported a dramatic improvement in addition to better scores on MMT. He regained ability to perform exercises including lifting weights, his hands returned to near normal function, and he reported that the greatest improvement was in his balance. Approximately 4 months after each treatment he started to weaken again and so was treated, as needed, every 6 months. The patient was asked to assess his condition at intervals before and after treatment using the form shown in *Figure 1*; his resultant scores are shown in *Figure 2*.

PROMS are also valuable for investigation of the natural history of neuromuscular disease. An example is the 15-item MG-specific QoL scale (MG-QoL15) that was developed from a larger set of 60 items and reduced to a core set.[6] In a Japanese study that included 640 consecutive patients with MG, MG-QOL15 scores correlated with prednisolone dose and disease severity.[7] MG-QOL15 scores for patients receiving ≤5 mg/day prednisolone were the same as those receiving no prednisolone whereas scores were significantly worse for those receiving >5 mg/day prednisolone.

Another example of a PROM that has provided insights into disease natural history is the Inclusion Body Myositis Functional Rating Scale (IBM-FRS), a 10-point disease-specific functional rating scale designed for use in patients with inclusion body myositis (IBM).[8] This test takes 15 minutes to perform, shows good correlation with other test measures, such as manual muscle testing (MMT), and accurately indicates disease status. The Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) is another validated PROM that has been used in multiple clinical studies as well as routinely in the clinic and is used more frequency than IBM-FRS.[9–12] The ALSFRS consists of four domains: gross motor tasks, fine motor tasks, bulbar functions, and respiratory function, which are not equally weighted. ALSFRS scores change in a linear fashion as ALS progresses whereas that is not fully established with IBM-FRS in IBM.

PROMS are also prominently included among data gathered in various patient registries, which also provide information on the natural history of neurologic disease.[13,14] PROMs form a central component of comparative effectiveness research initiatives across a range of different diseases;[15–17] they correlate well with assessments of HRQoL;[18] and indicate patient perceptions of illness and disease severity.[19,20]

PROMs help monitor a patient over time and can be instrumental in learning about an individual's perspective in the clinic. Assessment scales such as the MG-QOL15 are designed to involve patients and include them as part of the decision-making process. PROMs are designed so patients consider their progress in a structured manner, and are useful in many chronic neuromuscular diseases with manifestations that the patient is aware of such as: MG, CIDP, multifocal motor neuropathy (MMN), myopathies, and painful neuropathy.[5,21,22] They can be used to determine the efficacy of treatment, especially where improvements can be observed quickly. PROMs, however, are less applicable to diseases in which manifestations are not so clear to the patient or where improvement is not quickly discernible.[23-26] Such diseases may include diabetes, hypertension, inherited neuropathy, and dementia. In addition, conditions that develop slowly in which the effects of disease-modifying therapy have gradual and long-term effects are also less suitable for assessment using PROMs. PROMs are also less useful where there are large gaps between assessments. It is important therefore to consider the timing of treatment and follow-up before using PROMs and before selecting which one to use. Despite these limitations, PROMs are useful for many chronic conditions.[14,23,24,27]

Table 1: Key Patient-reported Outcome Measures for Neuropathies

Disease	Suitable Patient-reported Outcome Measures
Immune-mediated polyneuropathy	R-ODS, INCAT, CAP-PRI, SF-36, Neuro-QOL
Myasthenia gravis	MG-ADL, MG-QOL15, Neuro-QoL
Amyotrophic lateral sclerosis	ALS-FRS, ALS-QoL
Muscle diseases	IBM-FRS, MDHI, SF-36, Neuro-QoL, etc.

ALS-FRS = Amyotrophic Lateral Sclerosis Functional Rating Scale;[9] ALS-QoL = Amyotrophic Lateral Sclerosis quality of life scale;[41] CAP-PRI = Chronic Acquired Polyneuropathy – patient-reported index; IBM-FRS = Inclusion Body Myositis Functional Rating Scale;[42] INCAT = Inflammatory Neuropathy Cause and Treatment;[30] MDHI = Myotonic Dystrophy Health Index;[33] MG-ADL = Myasthenia Gravis Activities of Daily Living scale;[32] MG-QOL15 = 15-item Myasthenia Gravis Quality of Life Scale;[6] NeuroQoL = Neurology Quality of Life (system);[31] R-ODS = Inflammatory Rasch-built Overall Disability Scale;[5] SF-36 = Short Form 36-item scale.[28]

The PROMs used in Case Example 1 were a valuable and reliable means of monitoring MMN and identifying when a dose of intravenous immunoglobulin (IVIG) is necessary or a change in treatment plan is warranted. If a patient is being treated on an as needed basis, PROMs can alert the nurse or physician when clinical intervention is necessary, and in this way assist in managing symptoms to better control the condition.

A variety of useful PROMs exist for the assessment of neuromuscular disease (see *Table 1*).[28–32] Many of these are designed for specific diseases, such as the Myasthenia Gravis Activities of Daily Living (MG-ADL)[31] scale, whereas some are applicable to a variety of diseases such as the Short Form 36-item scale (SF-36).[28] Other scales include the R-ODS (uses include CIDP and Guillain Barre Syndrome [GBS], and Neurology Quality of Life [system] [NeuroQoL] short forms). These and other patient self-assessment instruments have been assessed and validated by the National Institutes of Health PROMIS network[33,34] and by the National Institute of Neurological Disorders and Stroke Common Data Elements (CDE) and are available from their websites.[35]

PROMs provide the patient perspective but are subjective—the clinician must decide how much weight to give each symptom/outcome measure versus clinical and laboratory findings. Patient circumstances (mood, environment, perception) may change over time and unrelated factors can affect PROM assessments. In addition, some patients seek attention or exaggerate symptoms, which creates artifacts and confounds results.

Despite these shortcomings, PROMs work well for most patients and add value to overall assessment. It is only necessary to choose one or two of the most appropriate scales. It is important to consider what parameters are required before selecting the scale. PROMs are useful in many clinical settings and prospective studies and are likely to be increasingly used as endpoints in clinical studies in the regular use for assessment and monitoring in the clinic.

Figure 1: Examples of Patient-reported Outcome Measure Questionnaires Used to Assess Neuropathy

A

Chronic acquired polyneuropathy – patient-reported index ("CAP-PRI") scale

Patient instructions: Please indicate how true each statement has been
(for example, over the past few weeks).

	Not at all	A little bit	A lot
	0	1	2
1. I am frustrated by my neuropathy.			
2. I am bothered by pain from neuropathy.			
3. I am off balance when walking because of my neuropathy.			
4. I have trouble getting dressed because of my neuropathy.			
5. I have trouble sleeping because of my neuropathy.			
6. I am bothered by limitations in performing my work (include work at home) because of my neuropathy.			
7. I have trouble driving because of my neuropathy.			
8. I am dependent on others because of my neuropathy.			
9. I am depressed about my neuropathy.			
10. I am falling because of my neuropathy.			
11. I am preoccupied with my neuropathy.			
12. I am unable to do all the leisure activities that I want to do because of my neuropathy.			
13. I am worn out because of my neuropathy.			
14. I have trouble eating because of my neuropathy.			
15. I have trouble doing activities around the house.			

Total score: _____

B

Subject number
Visit number for subject

Please indicate how true each statement has been
(over the past few weeks).

	Not at all	A little bit	Some-what	Quite a bit	Very much
	0	1	2	3	4
1. I am frustrated by my MG					
2. I have trouble using my eyes					
3. I have trouble eating because of MG					
4. I have limited my social activity because of my MG					
5. My MG limits my ability to enjoy hobbies and fun activities					
6. I have trouble meeting the needs of my family because of my MG					
7. I have to make plans around my MG					
8. My occupational skills and job status have been negatively affected by MG					
9. I have difficulty speaking due to MG					
10. I have trouble driving due to MG					
11. I am depressed about my MG					
12. I have trouble walking due to MG					
13. I have trouble getting around public places because of my MG					
14. I feel overwhelmed by my MG					
15. I have trouble performing my personal grooming needs					

MG-QOL15
Muscle and Nerve 2008;38:957-963.
Muscle and Nerve;2010;41:219-226.
Muscle and Nerve;2011;43:14-18

Total MG-QOL15 score

A. Chronic Inflammatory Demyelinating Polyneuropathy-Patient-Reported Index (CAP-PRI). B. 15-item Myasthenia Gravis Quality of Life Scale (MG-QOL15). Source: Gwathmey K and Burns T, personal communication; American Academy of Neurology (AAN), Washington DC, US, 2015, submitted for publication.

Opportunities to Improve the Immunoglobulin Patient Care Continuum

The continuum of care provided to patients receiving IVIG therapy is demonstrated in Case Example 2, which is a woman with CIDP.

The choice of treatment in this case of CIDP is between IVIG and corticosteroids. The decision requires consideration or treatment efficacy, side effects/risks, and the convenience of administration at home. Following the decision to administer IVIG at home, to maintain the patient continuum of care a Walgreens' pharmacist would perform an initial evaluation and counseling. This is designed to proactively reduce the risk for adverse events by determining a detailed medical history. This is important since IVIG therapy is associated with an increased risk for thromboembolism, renal insufficiency or failure, aseptic meningitis syndrome, anaphylaxis, and hemolytic anemia. Baseline PROM assessments of the patient revealed a continued decline in symptoms and QoL during the previous month, an ability to walk less than 10 feet, and always needing a cane or walker for mobility.

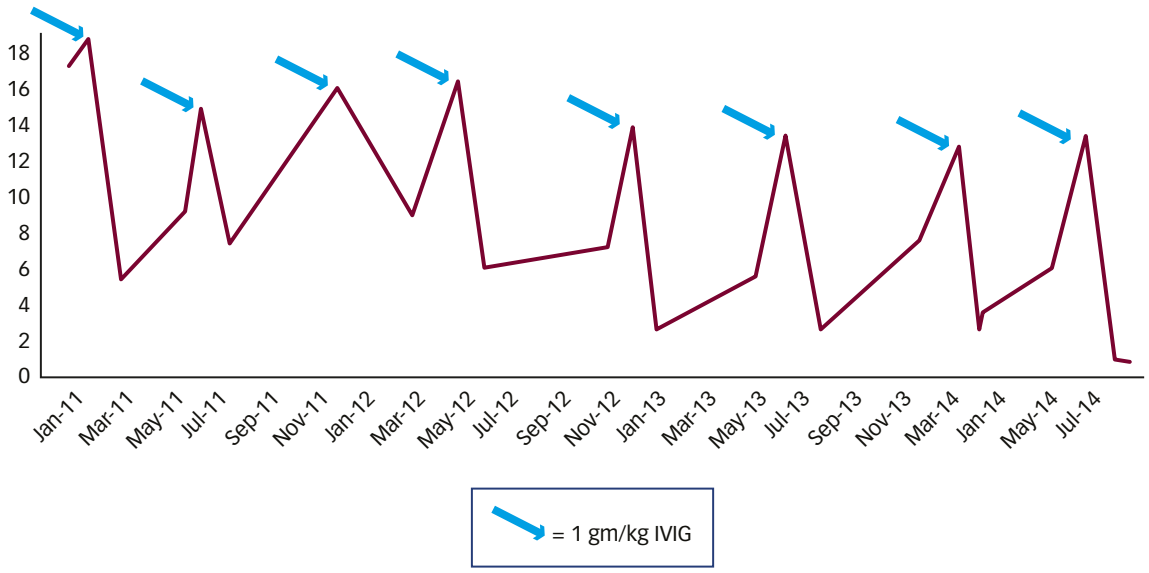
The continuum of care therefore begins with the treatment plan created by the clinician. Walgreens' clinical staff can then help define the risk for adverse events and establish baseline PROM scores. If serious risks are identified, they are reported to the physician and an alternative management plan is devised.

Walgreens PartnerPoint Clinical Management℠—Use in Case Example

The Walgreens IG program is a comprehensive IG management approach that utilizes a clinical management technology, Walgreens PartnerPoint Clinical Management.℠ PartnerPoint provides patient-specific clinical data, adverse event monitoring, clinical intervention tracking, and disease-specific outcomes. PartnerPoint provides transparent, consistent communication between the home infusion clinical team and the physician. Graphical reports trending clinical outcomes based on PROMs provide the physician tools that can be used to optimize care. This can assist the physician with managing dosing, pre-medication, adjunctive therapies, and IVIG cycle management, ultimately improving patient outcomes and demonstrating efficacy of treatment.

The value of Walgreens PartnerPoint Clinical Management℠ can be demonstrated by the above CIDP case example. Round two of the patient's

Figure 2: Chronic Acquired Polyneuropathy–Patient-reported Index (CAP-PRI) Scores in a 70-year-old Patient with 25-year History of Multifocal Motor Neuropathy Before and After Doses of Intravenous Immunoglobulin Given at Approximately 6-monthly Intervals



IVIG = intravenous immunoglobulin. Source: with permission, Professor T Burns.

treatment consists of 1 g/kg over 3 days every 4 weeks. One hour into the infusion the patient experiences headache, mild nausea, and flashing. The nurse halts the infusion for 30 minutes, repeats premedications, and decreases the infusion rate, but the headache persists. The pharmacist notifies the physician and for subsequent administrations the infusion rate is decreased and prehydration ordered.

The details of the adverse event are entered into the Walgreens PartnerPoint Clinical Management℠ system including type, severity score, management, and outcome. This information is communicated to the physician along with plots showing event incidence over time (see *Figure 3*). Subsequent infusions are tolerated with no further adverse events. Over 6 months, the patient stabilizes and improves. PROMs revealed marked improvements including Inflammatory Neuropathy Cause and Treatment (INCAT) scores decreasing to 1 in the arms and legs and in R-ODs, ambulation, and impression of health status (see *Figure 4*).

Walgreens PartnerPoint Clinical Management℠ has a number of advantages for the physician. These include improving the care continuum for the home IG patient and proactively avoiding or managing adverse events. This management system also ensures that PROMs and QoL measures are obtained monthly and that consolidated graphical reports are supplied to the prescribing physician on a regular basis or as requested. In the management of patients with neurologic disease the system provides the following advantages:

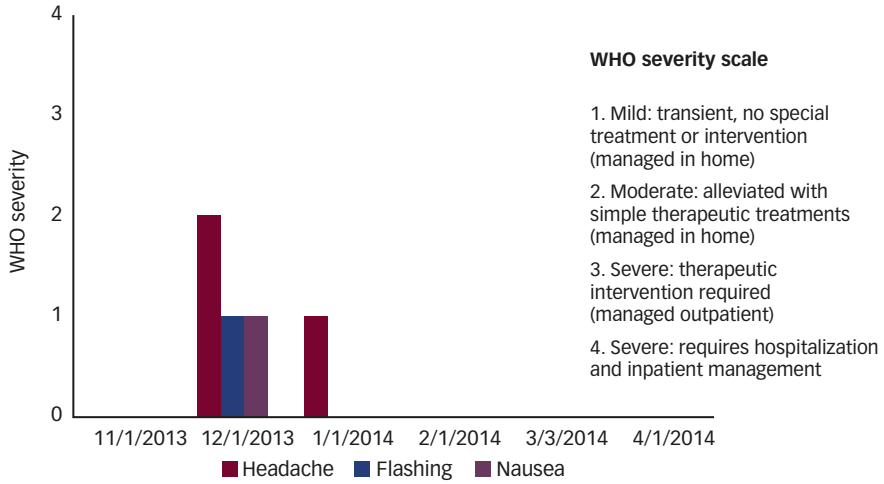
- Provides seamless integration from the clinic to the home.
- Supports patient management.
- Uses validated PROMs to assess response to therapy.
- Facilities short- and long-term clinical monitoring.
- Demonstrates short- and long-term treatment efficacy.
- Extends the physician's clinical reach.

Validation of Disease-specific Patient Reported Outcomes in the Home Environment

The use of IVIG therapy is increasing at a rate of 8–10 %/year with 25 % of this attributed to neurologic disease treatment.[36] Due to reduced costs, improved convenience, and better QoL findings,[37,38] an increasing proportion of this treatment is carried out in the home rather than the hospital outpatient setting. To enable this change, it is important that monitoring of efficacy and safety using PROMS is consistent with assessments performed by a clinician. There is a lack of comparative data supporting the validity of home versus clinical assessments, so a small study that included nine patients with CIDP and four with MMN was initiated to investigate consistency (see *Figure 5*).[39] Walgreens PartnerPoint Clinical Management℠ was used to gather data by IG-specialized pharmacists, who received disease-specific training as well as focused training in the use of the individual PROMs in order to ensure consistent and reliable reporting. This team of pharmacists conducted telephone interviews with patients that were synchronised with physician visits with a mean interval between paired assessments of 2.8 days.

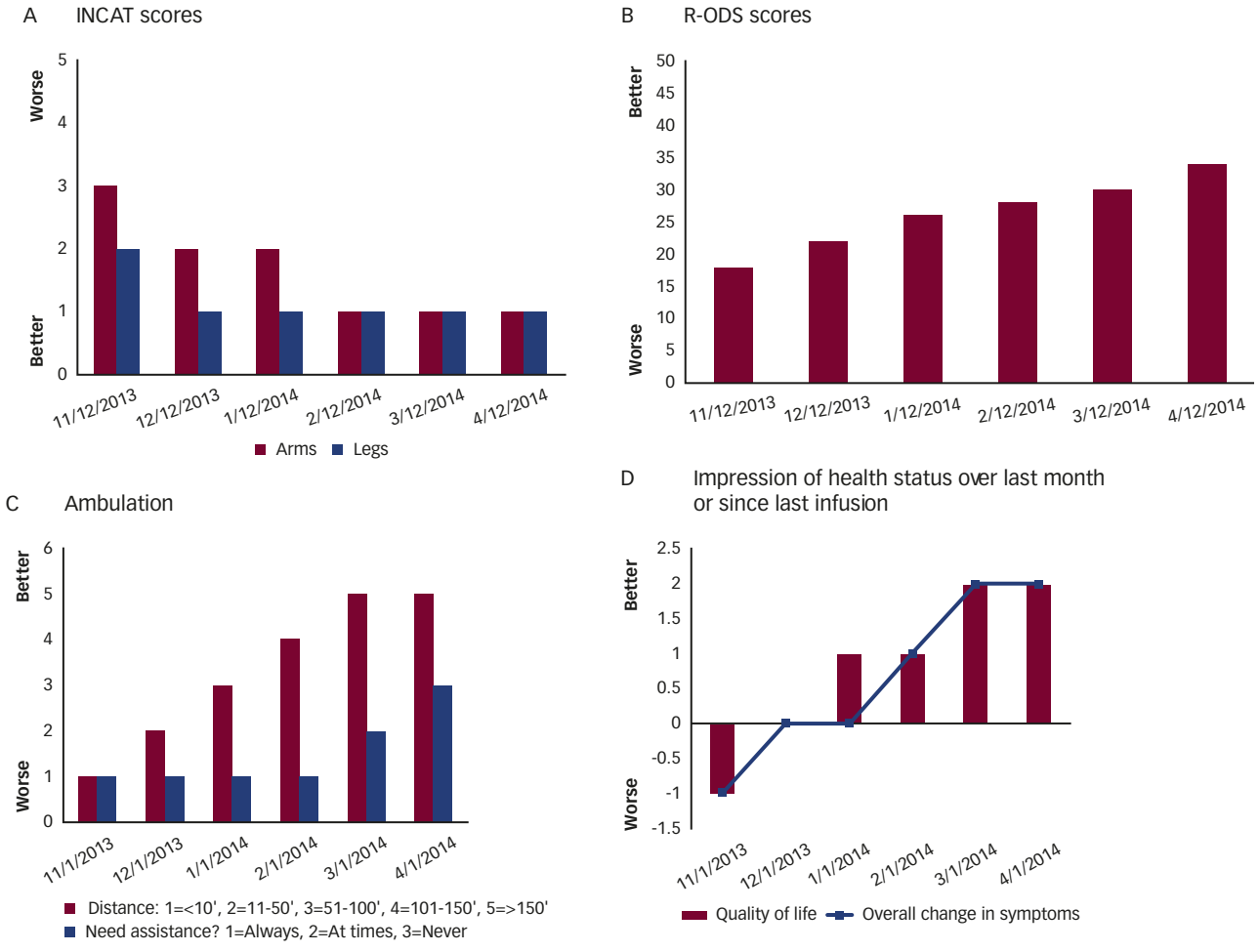
There were strong correlations and similarity in mean values between MD and home evaluations of R-ODS CIDP (Pearson Correlation Coefficient R=0.97) (see *Table 2*) and strong correlations and similarity of mean values in a combined analysis of both CIDP and MMN (see *Fsigure 5*) (24 observations, R=0.89). INCAT scores in leg function for both CIDP and MMN showed no significant difference between mean MD and home evaluations (p=0.34 and p=0.17, respectively) and a high correlation for combined analysis (R=0.86). However, mean INCAT scores for arm function showed significant differences for both CIDP and MMN (p<0.05 for both) with home evaluators reporting approximately 1 point less. An analysis of 0–10 pain scale scores of CIDP patients only showed a high correlation (R=0.85) with strong agreement between mean values (p=0.36) (see *Table 2*).

Figure 3: Adverse Event Monitoring using Walgreens PartnerPoint Clinical Management℠ of a Patient with Chronic Inflammatory Demyelinating Polyneuropathy Receiving Monthly Infusions of Immunoglobulin



WHO = World Health Organization. Source: Walgreen Co.

Figure 4: Patient-reported Outcomes in a Case of Chronic Inflammatory Demyelinating Polyneuropathy Receiving Infusions of Immunoglobulin—Reports Generated using Walgreens PartnerPoint Clinical Management℠



INCAT = Inflammatory Neuropathy Cause and Treatment; R-ODS = Inflammatory Rasch-built Overall Disability Scale. Source: Walgreen Co.

Case Example 2

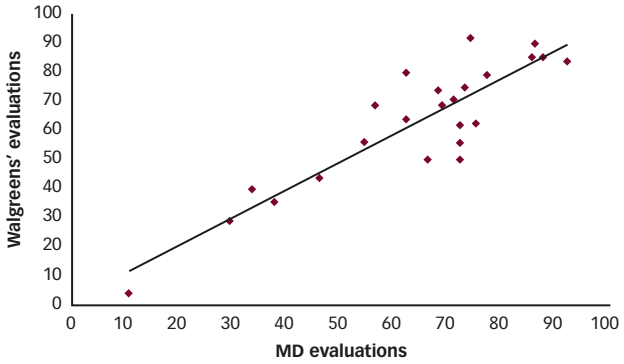
A 45-year-old woman with a history of well-controlled type 2 diabetes (glycated hemoglobin [HbA_{1c}] 6.3 %) and hypertension, received metformin and lisinopril. The patient presented with a 5-month history of slow progressive weakness in both arms and legs. She noticed difficulty in climbing stairs, buttoning shirts, and reported numbness and tingling in her hands and feet. Her mental status and cranial nerves were normal and she had normal hand strength and normal neck flexor and extensor strength. She had Medical Research Council (MRC) grade 4/5 strength in deltoids, biceps, wrist and finger extensors, interossei bilaterally. She also had MRC grade 4/5 strength in iliopsoas, hamstrings, quadriceps, foot and toe dorsiflexors bilaterally. Sensory examination demonstrated joint position sense and vibration in the toes. Deep tendon reflexes were absent throughout and gait was mildly wide-based using a cane. INCAT scores[30] were: three in arms and two in legs and the R-ODS score was 18. Nerve conduction studies and electromyography were consistent with acquired demyelination. Spinal fluid analysis demonstrated no white blood cells and an elevated blood protein level of 291 mg/dl. The diagnosis was consistent with CIDP. The patient was treated with IVIG 2 g/kg over 5 days (induction dose). Baseline blood urea nitrogen (BUN) and serum immunoglobulin A (IgA) were normal. Home infusion was ordered and completed successfully.

This study involved a small sample size: further investigations with a larger patient population are warranted to confirm the results. The inconsistency between mean INCAT arm scores could be resolved with improved assessor training for this instrument and further analysis to assess agreement of scores in this PROM is planned. However, the data show that the PROMs R-ODS, INCAT leg, and the 0–10 pain scale give almost identical results when patients with CIDP or MMN are evaluated either by a MD in the office-based setting or by a clinician in the home setting. In addition, there was strong correlation for combined CIDP and MMN measures of INCAT scores and arm and leg assessments (R=0.86, 0.66, and 0.84, respectively). This indicates that Walgreens PartnerPoint Clinical Management℠ can be used to reliably assess patients with neuromuscular disease receiving IVIG in the home setting. In addition, Walgreens Partnerpoint Clinical Management℠ supports the growing trend of increased use of IVIG away from the hospital setting.

A Retrospective Analysis of Patient-reported Outcomes for 34 Patients with Stiff Person Syndrome Receiving Home IVIG Infusions

IVIG is used to treat a range of neuromuscular disorders, however, there are limited data supporting home treatment of some of these diseases. An example is stiff person syndrome (SPS) in which PROMs have been shown to be valuable in assessing disease status and treatment efficacy. The PROMS used in this study are not validated measures but they may be valuable within the assessment process. This was demonstrated in a retrospective study of 34 patients with SPS receiving IVIG. PROMs were analysed for 18 patients with more than two evaluations more than 30 days apart (see *Figure 6*).[40] Patients had a mean of 5.9 evaluations and an average of 7.9 months between first and last infusion. Evaluations of arm, trunk and leg stiffness, ADL, heightened sensitivity to stimuli, balance, sleeping, and cramping all showed trends towards improvement that were

Figure 5: Correlation between Clinician (MD) and Pharmacy (Walgreen Co.) Evaluations of Combined Inflammatory R-ODS scores in patients with CIDP or MMN



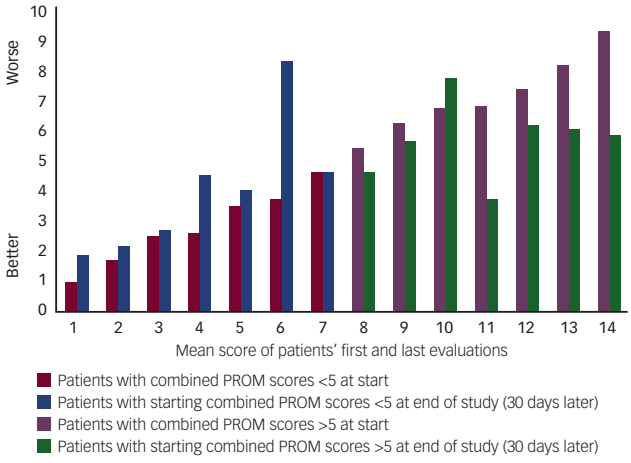
Number of observations = 24; Pearson correlation coefficient, R=0.89. CIDP = chronic inflammatory demyelinating polyneuropathy; MMN = multifocal motor neuropathy; R-ODS = Inflammatory Rasch-built Overall Disability Scale. Source: Ayer et al., 2014.[39]

Table 2: Agreement in Mean R-ODS Scores in Patients Assessed by a Clinician or by a Walgreens' Operative in the Home Setting

Assessment Conducted by	Number of Observations	Mean R-ODS Score	Standard Deviation	p Value
Multifocal Motor Neuropathy				
Walgreens	10	35.10	7.98	0.61
MD	10	36.73	4.82	–
Chronic Inflammatory Demyelinating Polyneuropathy				
Walgreens	14	27.57	11.48	1
MD	14	27.57	11.19	–
Pain Scale				
Walgreens	14	1.71	2.84	0.36
MD	14	2.00	2.88	–

R-ODS = Inflammatory Rasch-built Overall Disability Scale.

Figure 6: Combined Patient-reported Outcome Measures in Patients (n=14) with Stiff Person Syndrome Before and After IVIG Treatment—An Initial Score of >5 is Predictive of Treatment Response*



**p=0.04. Scores were derived from assessments of arm, trunk, and leg stiffness, activities of daily life questions, heightened sensitivity to stimuli, balance, pain, sleeping, and cramping before and after intravenous immunoglobulin (IVIG) treatment. PROM = patient-reported outcome measures. Source: Ladha et al., 2014.[40]*

nonsignificant (p=0.13–0.99). The measures used, however, may not be have been sufficiently sensitive to detect significant response to therapy, or the patient subjective assessment may be have been optimistic.

The improving trends seen on PROMs were confirmed by the patients' subjective impression of current health status: 94 % of patients reported improvement or stable status since the last infusion (p=0.03). In addition, 46 % of patients' self-assessments agreed with the PROM score change, 21 % partially agreed (between same-improve, or stable-decline, for example), and 33 % disagreed (improve-decline). An analysis of combined scores in a subset of patients (n=14) showed that a mean initial combined score of >5 predicted a treatment response (p=0.04) (see *Figure 6*). Currently, there are no PROMs specifically designed for SPS but the results indicate that further work to define and validate PROMs for this disease are warranted and further explore assessments that may identify suitable candidates for IVIG treatment.

Discussion and Conclusions

The case reports and studies discussed indicate that PROMs and proven patient management systems add value to the traditional patient assessment. PROMs are increasingly important components in the management of patients with neurologic disease who are receiving IVIG in the home setting. These assessments are simple to perform, most taking only 4–5 minutes, and can be performed even in the busiest clinics and at home. When using PROMs, however, it is essential to recognize which changes are clinically meaningful. Changes of >1 in the INCAT, for example, are regarded as significant. However, it is also important that PROMs are considered as part of a larger picture that includes standard clinical measures and the physician perspective. Trained nurses who visit patients at home may be able to perform various physical measures in addition to collecting PROM results. PROMs are important but are not replacements for objective clinical examinations by a physician.

Home administration of IVIG for a range of neurologic diseases will continue to grow in the future. This trend increases the importance of PROMs as a means of tracking patients' progress remotely. Such monitoring necessitates validated outcome measures and confidence in them. This also requires reliable patient management and clinical reporting systems such as those in the Walgreens PartnerPoint IG program. PartnerPoint℠ provides clinicians with patient-specific therapy outcome reports on a regular basis and following adverse events. Such systems establish a flow of information from the nurse to the pharmacist to the physician, maintaining awareness by all parties involved in the patient care continuum. PROMs have been developed for neuromuscular diseases such as CIDP, MMN, and ALS, but there remains a requirement to develop assessments specific to neurologic diseases, such as SPS, to monitor the most appropriate variables and guide management. Data from larger studies will help validate PROMs as a cornerstone in IVIG administration and help to demonstrate therapeutic efficacy in the home infusion population. ■

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