Optimizing the Use of Outcome Measures in Chronic Inflammatory Demyelinating Polyneuropathy

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The challenges encountered during the assessment of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) are many. Ideally, CIDP outcome measures capture impairments in disability, strength, and sensory dysfunction, and quality of life (QoL). A number of outcome measures have been validated for this purpose. Disability outcomes include the adjusted inflammatory neuropathy cause and treatment (INCAT) disability score, INCAT overall disability sum score (ODSS), and overall neuropathy limitations scale (ONLS). A more sensitive disability score, the inflammatory Rasch-built overall disability scale (I-RODS), has also been validated for use in clinical trials and may better capture clinically meaningful changes in those with CIDP. Strength and sensory impairment can be assessed in a number of ways, including the INCAT sensory subscore (ISS), Medical Research Council sum score, and Martin vigorimeter or Jamar dynamometer grip strength. However, the feasibility of applying and interpreting these measures during routine daily practice has been questioned. Furthermore, these outcome measures may not reflect other factors that can impair QoL in those affected by CIDP, such as pain and fatigue. A valid, reliable, and responsive composite measure that addresses all aspects of impairment faced by patients with CIDP remains an unmet need in clinical practice.

Keywords

Chronic inflammatory demyelinating polyneuropathy, disability, impairment, outcome measures, grip strength

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired immune-mediated disease that evolves in a progressive or relapsing pattern over months to years. Although "typical" CIDP is characterized by symmetric proximal and distal motor and sensory deficits, it is now recognized that multifocal (asymmetric), distally predominant, pure sensory, and pure motor variants also fall within the CIDP spectrum. First-line treatment options for CIDP include corticosteroids, intravenous immunoglobulin (IVIG), and plasmapheresis (plasma exchange).[1] For patients refractory to first-line options or those chronically dependent on high-dose first-line therapy, no evidence-based treatment recommendations exist. Cytotoxic immunosuppressant drugs are sometimes utilized.[2] Close follow-up care is essential for treatment administration and optimization. Patients treated with IVIG or plasma exchange need regular treatment visits to maintain therapeutic efficacy, typically every few weeks. Many patients with CIDP remain on such treatment for years. While, in some, chronic immunotherapy is justified on the basis of well-defined clinical changes indicative of active disease (e.g., treatment-related fluctuations or relapse); in many patients, treatment is driven by subjective feelings of benefit without objective evidence of improvement in motor and sensory deficits or disability.[3] There is an opportunity to supplement periodic outpatient clinical visits with currently available objective measures as a means to improve confidence in treatment-induced disease modification, optimize therapy, and justify treatment dependence for those on chronic therapy.

Evaluating responses to treatment in CIDP may be difficult. The absence of a clear definition of treatment response, in part due to the heterogeneous nature of CIDP and its variants, is one challenge. The many scales that have

Table 1: Overview of currently validated scales suitable for use in CIDP

Scale	Number of Items	Scoring Range	Estimated Time to Complete	Key Measures	Validated	Patient-versus Physician-reported
INCAT	10	0 to 10	3–5 min	Arm and leg disabilities scores, overall score is sum of the two	Outcome measure in ICE study, n=117[8]	Patient
ODSS	10	0 to 5 (upper limb) and 0 to 7 (lower limb)	3 min	Arm and leg disabilities scores, overall score is sum of the two	Clinical study, n=113 (22 with CIDP)[12]	Patient
ONLS	13	0 to 5 (upper limb) and 0 to 7 (lower limb)	3 min	Same as ODSS, but question "Does the patient have difficulty walking?" has been changed to "Does the patient have difficulty running or climbing stairs?"	Clinical study, n=100 (42 with CIDP)[14]	Patient
RODS	24	Raw RODS score (0–48) transformed to final score 0–100	3–5 min	Upper and lower limb disability, questions range from ability to "read a book," "eat," or "brush teeth" to "dance", "stand for hours," and "run." Participants are asked to indicate if they can easily perform the task, perform it with difficulty, or are unable to perform the task at all	Preliminary study, n=294 (80 with CIDP)[16] and comparison with ONLS, n=115 (59 with CIDP)[17]	Patient
GAITrite®	NA	Percentage scores recorded	*	Gait parameters: Velocity, cadence, swing phase, double support time, stance phase	Prospective evaluation, n=9, all with CIDP; study in healthy adults, n=2,523	Physician
TUG	NA	Timed activity test	2–3 min	Time taken to stand up from a chair, walk a short distance, turn around, return, and sit down again	Validated in elderly people (not with CIDP), n=60[26]	Physician
10-meter walk test	NA	Timed activity test	*	Time taken to walk 10 meters	Comparison with other performance tests, n=12, all with CIDP[28]	Physician
Grip strength	NA	Instrument-based scale	3–5 min	Grip strength	Analysis of ICE trial data, n=117[35]	Physician
FSS	9	9–63	3–5 min	Questions relating to fatigue severity and the impact of fatigue on activities and lifestyle	Prospective evaluation, n=113 (22 with CIDP)[38]	Patient
Rasch-based FSS	7		2–3 min	As in FSS but with 4 response categories	Prospective evaluation, n=192[40]	Patient
SF-36	36	8 scaled scores, each directly transformed into a 0–100 scale	*	Physical functioning (10 items), role functioning—physical (4), role functioning—emotional (3), social functioning (2), body pain (2), mental health (5), vitality (4), general health perception (5), and change in health	Compared with other measures in study, n=144 (23 with CIDP)[43]	Patient
CAP-PRI	15	Single score comprising 4 life domains	5–10 min	Physical function, social function, pain, emotional well-being	Multicenter validation study, n=63 (CIDP; MMN; monoclonal Ab-associated neuropathy)	Patient

**No estimated time given although most assessments will be finished in approximately 5 minutes. The exact time taken to perform tests depends on the severity of a patient and the experience of the practitioner collecting the measure. CAP-PRI = Chronic Acquired Polyneuropathy Patient-reported Index; CIDP = chronic inflammatory demyelinating polyneuropathy; FSS = Fatigue Severity Scale; ICE = Immune Globulin Intravenous CIDP Efficacy; INCAT = Inflammatory Neuropathy Cause and Treatment; MMN = multifocal motor neuropathy; ODSS = INCAT overall disability sum score; ONLS = Overall Neuropathy Limitations Scale; RODS = Rasch-built Overall Disability Scale; TUG = Timed Up and Go; SF-36 = Short Form–36.*

been developed to measure strength impairment, sensory dysfunction, and disability emphasize the many modalities in which treatment response can be objectively assessed.[4] Established outcome measures are typically employed in clinical studies in order to ensure comparability between trials. Outcome measures are considered appropriate for use if they demonstrate high validity (i.e. they are able to measure the intended parameter) and reliability (i.e., they measure the parameter in a reproducible manner) and are sensitive to change.[3] However, many measures used in clinical trials are not accessible or feasible for daily practice. This is a critical factor when evaluating patients with CIDP. This article aims to review currently used and validated outcome tools in CIDP, assess their suitability for use in everyday clinical practice, and highlight other potential tools that might be helpful in the routine clinical settling.

Validated scales for assessing outcomes in CIDP

A number of different outcome measures that are appropriate for use in CIDP are summarized in *Table 1* and described in detail below.

Inflammatory neuropathy cause and treatment disability scale and sensory subscore

From a consensus meeting on outcome measures in inflammatory neuropathies, the level of disability emerged as the primary measure for assessing treatment efficacy.[4] The inflammatory neuropathy cause and treatment (INCAT) disability scale captures upper and lower limb dysfunction separately on a scale of 0 to 5, which are then added together for a total composite score ranging between 0 and 10.[5] Lower scores indicate no or minimal disability (no arm dysfunction or walking abnormality); higher

scores indicate more disability (no purposeful arm movement or restricted to wheelchair). An adjusted INCAT disability score has been used in multiple clinical trials, including the largest CIDP trial performed to date, the immune globulin intravenous CIDP efficacy (ICE) study.[6,7] The adjusted INCAT disability score is identical to the INCAT disability score with the exception that changes in upper limb function from 0 (normal) to 1 (minor symptoms) are excluded. This exclusion was made because upper limb changes from 0 to 1 (minor symptoms in the fingers which do not impair any functional activities) were not judged by regulatory agencies to be clinically significant in all patients. This measure showed statistically significant differences in favor of patients treated with human IVIG, 10% caprylate/chromatography purified, compared with patients who received placebo. The most common adverse reactions were headache, fever, chills, hypertension, rash, nausea, and asthenia, and the most serious adverse reactions in clinical studies was pulmonary embolism (PE) in 1 subject with a history of PE.[7]

The INCAT sensory subscore (ISS) has been evaluated for uniformity in assessing sensory deficit in immune-mediated polyneuropathies.[5] The scale assesses light touch, pin-prick, vibration, and joint position sense in distal and proximal upper and lower limb areas as well as 2-point discrimination at the index finger. In a psychometric validation study, moderate to good validity was obtained for the ISS combined with acceptable internal consistency and inter- and intra-observer reliability. Standardized response mean scores for the ISS were high, indicating favorable responsiveness.[5] Although the ISS has been recommended for evaluation of sensory deficit in clinical practice and in trials, it may not be the optimal choice for all types of inflammatory neuropathy. In clinical trials of rituximab for anti-myelin-associated glycoprotein (anti-MAG) neuropathy, no ISS changes were found, suggesting either treatment failure or lack of ISS sensitivity to change.[8]

The major strengths of the INCAT disability scale and the INCAT ISS are validity and reliability. Although the INCAT disability can be obtained quickly (good feasibility in clinical practice), the same cannot be said with the ISS.[5] Other advantages include the ability to evaluate both upper and lower limb dysfunction (INCAT disability) and to quantify sensory impairments (ISS). The weaknesses of both, as with all multi-item composite ordinal measures, are that the individual components of the sum scores do not have equal weight and cannot be represented linearly. A 1-point change in score may have different clinical significance depending upon where in the scale that change occurs. Concerns have also been raised regarding the methodologic quality of validation studies, including their failure to fully capture activity limitations. The INCAT disability scale poorly measures proximal arm weakness and fails to capture subtle changes in gait stability and running. As such, the scale has poor sensitivity for detection of subtle but clinically meaningful change,[9] which is again highlighted in a study of anti-MAG neuropathy.[8] Such changes may be better addressed by the overall disability sum score (ODSS) or the overall neuropathy limitations scale (ONLS).

Overall disability sum score and overall neuropathy limitations scale

The ODSS was the first scale designed to quantify the limitations of patients with immune-mediated peripheral neuropathies.[10] The ODSS focuses on the function of the upper and lower limbs and consists of a checklist for interviewing patients. It is scored from 0 to 5 on upper limb function and from 0 to 7 on lower limb function, where a score of 0 indicates no limitations (the ceiling of the scale) and a score of 5 or 7 indicates no purposeful movement. Unlike the 10-point INCAT disability score, the ODSS better captures lower limb disability at both ends of the severity spectrum, effectively broadening the floor and ceiling of the scale.[4]

A study of 113 clinically stable patients (83 with Guillain-Barré syndrome [GBS]; 22 with CIDP; 8 with a gammopathy-related polyneuropathy) compared the overall (arm plus leg) ODSS with 2 other measures of disability (Hughes' functional scale [f score] and Rankin scale), and 3 impairment measures (Medical Research Council sum score [MRC-SS]; sensory sum score; grip strength using the vigorimeter). The authors concluded that the ODSS was simple to use and demonstrated high validity, reliability, and responsiveness in CIDP, providing a better evaluation of impairment leading to disability than the other measures.[10] In another study, the ODSS was compared with other disability scales in 20 consecutive patients with recently diagnosed GBS (n=7) or CIDP (n=13). The ODSS showed higher correlation with short form-36 (SF-36) domains and patients' own perception of their clinical condition than other disability scales.[11] The authors concluded that the ODSS was a useful primary outcome measure for clinical trials investigating CIDP therapies,[11] an opinion that is shared by many neurologists.[4]

One limitation of the ODSS is its failure to measure difficulties with climbing stairs and running. Therefore, a modified peripheral neuropathy measure, the ONLS, was devised.[12] Specifically, the ODSS item "Does the patient have difficulty walking?" was changed to "Does the patient have difficulty walking, running or climbing stairs?" The remaining scoring criteria are not different from the ODSS. This small difference makes it more difficult to improve from 1 to 0, reducing the ceiling effect of the ODSS. In turn, this modification may reduce the responsiveness of the ONLS. In a study of patients with GBS (n=12), CIDP (n=42), chronic idiopathic axonal polyneuropathy (n=11), paraprotein-associated demyelinating neuropathy (n=13), Charcot-Marie-Tooth disease (n=9), and other neuropathies (n=13), the 2 scales correlated strongly with each other. They also correlated with the Role Limitation Physical Subscale of the Medical Outcome Study SF-36 health status scale (a quality of life [QoL] measure) in patients with GBS and CIDP, but not in patients with other forms of peripheral neuropathy. This may reflect the more acute progression of deficits in patients with GBS and CIDP resulting in greater functional limitation, but no firm conclusions can be drawn from such small subgroups.[12]

The ODSS and ONLS are among the best measures of disability as an outcome measure in clinical trials and are useful in a routine clinical environment. Like the INCAT disability score, the outcomes can be obtained rapidly and thus are feasible for routine clinical care. They are ordinal measures and cannot be represented linearly like the INCAT disability score. Furthermore, they have not been used to assess outcomes in large cohorts of patients with CIDP.

The Rasch-built overall disability scale

The INCAT scales are based on classic test theory, i.e., multi-item measures that assume all components have equal weight and therefore equal relevance.[13] Physicians often incorrectly interpret a 1-point response change for an item (e.g., from 0 to 1 as equivalent to a 1-point change from 2 to 3). However, since the response options are ordinal based, the true distance between the response categories is not known and may be unequal. The Rasch statistical methodology overcomes these shortcomings. Rasch is a mathematical model that aims to give a true reflection of disease impact based on the probability that a person will be able to complete an

item, dependent on the item difficulty and the person's level of ability.[14] For example, it is logical to assume that walking up a flight of stairs will be a much more difficult task to accomplish than washing one's face. The Rasch-built overall disability scale (R-ODS) for immune-mediated peripheral neuropathies is a patient-based, linearly weighted scale that captures activity and social participation limitations in patients with CIDP, GBS, and polyneuropathy associated with a monoclonal gammopathy of undetermined significance (MGUSP).[14] The assessment includes 24 questions that address upper and lower limb disability. These range in difficulty from ability to read a book, eat, or brush teeth to dance, stand for hours, and run. Participants are asked to indicate if they can easily perform the task, perform it with difficulty, or are unable to perform it at all. Both the ability of the patient and the perceived difficulty of a task are tallied for a raw R-ODS score that ranges between 0 (complete disability) and 48 (no disability). The resulting raw R-ODS score can then be transformed to a final R-ODS score ranging from 0 to 100. Of note, R-ODS scale developed for multifocal motor neuropathy (MMN) is tailored to that condition and should not be confused with the RODS disability score for CIDP, GBS, and MGUS neuropathy.[15]

A preliminary study assessed R-ODS in 294 patients who had experienced GBS in the past (n=174) or had stable CIDP (n=80) or MGUSP (n=40), and reported good reliability and validity.[14] Another advantage of R-ODS (now referred to as I-RODS or inflammatory-RODS) is the ability to better capture clinically meaningful changes over time compared with the INCAT-ONLS in patients with GBS (n=55) and CIDP (n=59).[16] The I-RODS offers a more sensitive outcome measure than INCAT-ODDS or OLNS, and it has been proposed as the primary measure of disability in future clinical trials involving patients with GBS and CIDP.[17]

Feasibility is both an advantage and potential limitation of the I-RODS. Although the scale can be completed quickly with minimal training, the resulting raw RODS score is not designed to be interpreted directly but rather items should be transformed to the linear weighted final R-ODS score using a conversion table.[14] Even then, intra-patient I-RODS minimal clinically important differences are difficult to interpret.[16] Another potential disadvantage is the observation that in different geographical regions, item bias was observed in 6 of the 24 (25%) items, which suggests that the scale requires further cross-cultural exploration.[17]

Gait assessments

The traditional scales used to analyze gait parameters in clinical conditions are carried out by specialists who observe the quality of a patient's gait by making him/her walk. This is sometimes followed by a survey in which the patient is asked to self-evaluate the quality of his/her gait. The disadvantage of these methods is that they are subjective, raising concerns of accuracy and precision as well as reproducibility. Newer gait analysis devices and techniques allow a more objective evaluation of gait, resulting in more meaningful and reliable data. This reduces the error margin caused by subjective techniques.[18]

Gait (GAITrite®)

GAITrite® (CIR Systems Inc., New Jersey, US) is an electronic walkway with embedded pressure sensors. Its value in CIDP was demonstrated in a prospective evaluation of 9 newly diagnosed patients. The findings suggested that the GAITrite walkway detects changes following treatment that correlate with changes in the MRC score.[19] Further, a prospective evaluation of 20 patients with CIDP, following a 3-month course of IVIG treatment, indicated that gait parameters, as measured by GAITrite, may provide a sensitive clinical tool.[20] Increases in velocity, cadence, and swing phase percentage and reductions in double support time and stance phase percentage were noted after treatment. Changes in these specific parameters suggest a pattern of objective gait recovery that may reflect improvement in strength, proprioception, and coordination following treatment.

The GAITrite system has the advantage of being portable and easy to store and use, as well as being relatively inexpensive. In a preliminary evaluation, its validity compared with other methods was good, and it was capable of measuring both temporal and spatial parameters of gait at a variety of speeds.[21] A study of 25 healthy adults showed good validity and retest reliability, although the repeatability was more variable at slow speeds.[22] The use of the GAITrite has also been validated in children.[23]

Wearable sensors

Wearable sensor systems make it possible to analyze gait during a person's routine daily activity. Sensors are placed on various parts of the patient's body, such as the feet, knees, or hips, and measure various characteristics of gait. A number of different sensors are available, including force sensors, accelerometers, gyroscopes, extensometers, inclinometers, goniometers, active markers, and electromyography, but none have been validated in studies of patients with CIDP.[18]

Timed up and go test

The Timed Up and Go (TUG) test involves a patient standing up from a seated position, walking a short distance, turning around, returning, and sitting down again.[24] In a study of 60 elderly patients (mean age 79.5 years) it was found to be reliable (inter-rater and intra-rater) and correlated well with log-transformed scores on the Berg Balance Scale, gait speed, and Barthel Index. It also seemed to predict the ability to walk outside alone safely. The test is quick and requires no special equipment or training, and can be used in routine evaluation.[25] It also includes getting up from a chair, walking, and turning, which incorporates a number of aspects of lower leg function. The limitation of the TUG test is the absence of validity and sensitivity to change data in patients with inflammatory neuropathy.

10-Meter walk test

The 10-Meter Walk Test (10MWT) assesses walking speed. In a study of 43 healthy adults (mean age 84.3±6.9 years) the 10MWT was compared with the 4-Meter Walk Test (4MWT). Although both gait speed assessments had excellent test retest reliability with similar standard error of measurement across measurement methods and minimal detectable change values, the 4MWT did not give a high enough degree of concurrent validity, and the discrepancy was large enough to potentially mask meaningful changes in gait speed over time if both methods were used interchangeably.[26] The 4MWT has not been tested in patients with CIDP. In a study of 12 patients with CIDP, the 10MWT was used alongside a performance-based body function test, a self-reported activity test, and a self-reported functioning test. While the 10MWT was considered useful in assessing gait in patients with CIDP, a clear relationship between body activities and functioning was not found, highlighting the importance of assessing multiple parameters in investigating inflammatory neuropathies.[27] In addition, some patients with CIDP and MMN performed the 10MWT with ease as they experienced difficulties only with walking long distances. This suggests that an extended walking test should also be performed.

Figure 1: Vigorimeter (A) and Jamar Handgrip Dynamometer (B)

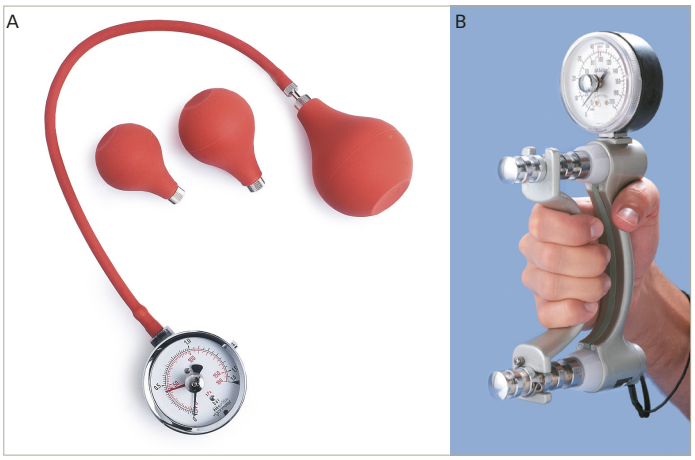

Figure 1A reused with permission from Albert Waeschle. Figure 1B reused with permission from Patterson Medical Ltd.

The 6-minute walking test is another established and validated assessment of walking ability. It has been found to correlate with established outcome measures in spinal muscular atrophy, and is sensitive to fatigue-related changes but has not been assessed in patients with CIDP.[28]

In summary, objective gait analysis is a potentially important outcome measure in CIDP. Currently available measures, in particular TUG and 10MWT, may be both reliable and feasible in the routine clinical care setting, but their validity in CIDP has not yet been established. When using gait as a measure of outcome in CIDP it is important to keep in mind that simply assessing the ability to walk is an inadequate representation of a patient's overall function.[29] As such, quantifying gait impairment with reliable and valid assessments is needed, as is combining gait impairment with other validated clinical outcome tools in patients with relatively preserved gait but substantial disability in other areas.

Grip strength

Grip strength has largely superseded older methods of assessment of muscle strength, such as the MRC-SS.[30,31] Grip strength can be assessed using various devices such as the Jamar® hand-held dynamometer (Lafayette Instrument, Indiana, US) and the Martin vigorimeter (Martin, Tuttlingen, Germany)[6] (see *Figure 1*). Both provide a quantitative objective measure of grip strength and an instant measure of strength impairment.[32] The dynamometer is used more commonly in the US and the vigorimeter in Europe. A study comparing the vigorimeter versus Jamar dynamometer in immune-mediated neuropathies, including CIDP, revealed that significantly more patients preferred the vigorimeter, largely based on hand comfort during testing.[33] Validity, reliability, and responsiveness were similar between the two tools.

The advantages of testing grip strength are many. It is a quantifiable outcome measure that can be collected quickly and easily, is relatively objective, and is less susceptible to bias than other outcome measures. In a systematic analysis of data from patients with CIDP in the ICE study, both vigorimeter-measured grip strength and the INCAT disability scale showed significant improvement at week 6. Dominant hand grip strength, however, showed a statistically significant improvement earlier than INCAT, at day 16 and at day 21 (p=0.018 and p=0.021) and also captured deterioration earlier.[34] Although some have raised concerns that in routine clinical practice a patient's grip strength may be poorly representative of lower limb or proximal predominant weakness[35] in a randomized controlled trial, grip strength was shown to provide objective documentation of global neurologic status in patients with CIDP, not limited to the upper limb or exclusively motor function.[34] Disadvantages include the expense of purchasing special equipment, the need to supervise the measure to assure standardized technique, and limited utility in patients with severe hand weakness (<5 kg).

Manual muscle strength testing and isokinetic strength testing

The MRC developed the manual muscle test (MMT) to assess muscle weakness in daily clinical practice, The MMT is straightforward to perform, allows for muscle strength sampling in proximal and distal upper and lower limb areas, and does not entail the use of expensive instruments. A drawback of this test is its lack of sensitivity for the detection of mild to moderate weakness of large muscle groups when symmetrical weakness is present.[36] Examples of such muscle groups include the ankle plantar flexors, knee extensors, and hip flexors. In addition, the MMT is highly dependent on the skills and experience of the assessors, which means that the inter-rater reliability can be low.[36] By contrast, isokinetic testing is a quantitative measurement of muscular contraction that allows objective, valid, and reliable measurement of the force produced by a skeletal muscle during exercise at constant velocity and when accommodating resistance.[37,38] Isokinetic testing may be better suited to detect small changes in muscle strength over time compared with MMT. In addition, isokinetic testing may be better suited to quantitate how much resistance muscles take when graded 4/5. Isokinetic testing protocols, described by Harbo et al.[39] have been used as an outcome measure in studies exploring the safety and efficacy of subcutaneous administration of immumoglobulins in CIDP.[40-42] Cost and space constraints limit the utility of isokinetic dynamometry in the routine clinical care setting. The assessment also can be timely to perform and requires expertise on the part of the evaluator to become familiar with the testing protocols. Some muscles, in particular muscles that are very weak or very distal, may not be appropriately assessed with isokinetic dynamometry.

Fatigue severity scale

Fatigue is a complex entity that is sometimes a debilitating symptom in patients with immune-mediated polyneuropathies. In a noninterventional study, changes in depression and fatigue dynamics are being assessed in patients with CIDP.[43] Early results suggest that fatigue imparts a high burden on patients with CIDP and should be considered a relatively independent and potentially disabling symptom in patients with CIDP.[44]

The fatigue severity scale (FSS) is one available tool to measure fatigue.[44] FSS is a patient self-assessment questionnaire that measures fatigue severity and impact on activities and lifestyle by asking participants to respond to 9 separate items. Responses are scored on a 7-point scale (1 = strongly disagree, 7 = strongly agree; total score range 9–63, where a higher score indicates more fatigue). The FSS has been validated in a large patient cohort and was considered simple to use and showed excellent internal consistency and reliability.[45] In a cohort of 133 patients with immune-mediated polyneuropathies (22 with CIDP), "severe" fatigue (FSS scores ≥95th percentile values in controls) was present in 80% of

patients. Variables such as age, disease duration, and INCAT sensory sum score were not significantly associated with fatigue. One limitation of the 9-item FSS is its ordinal scale. A newer, 7-item linearly weighted Rasch-built scale, with 4 response categories for each item, has been developed and assessed in 192 patients with immune-mediated neuropathies. It showed good reliability and validity for patients with CIDP, but further validation of this scale is needed.[46]

Although fatigue is an important factor in determining QoL in CIDP, experts generally agree that fatigue as an isolated outcome is not an appropriate measure for assessing treatment response. Fatigue can be present in CIDP patients with normal general strength and sensation[44] and, like fatigue in GBS,[47] might persist as a residual deficit even in those with inactive disease. Furthermore, fatigue may be influenced by other, non-CIDP-related factors such as age, medications, comorbid disease, and general conditioning. In summary, FSSs represent a valid and sensitive measure of assessment, but represent only one component of a multifaceted disease.

Quality of life

Experts have emphasized the importance of QoL measures in the assessment of inflammatory neuropathies. Factors such as low motivation, fatigue, pain, and depression can affect patients' confidence to focus on the challenges of recovery.[17] A neuropathy-targeted health-related QoL measure based on the RAND-36 Health Survey was described in 2000.[48] This measure demonstrated acceptable validity, reliability, and responsiveness in patients with diabetes-related neuropathies and was considered appropriate for patients with CIDP,[48] although it has not been widely adopted.

The SF-36 is one of the most widely used generic QoL measures but does not address specific QoL issues in CIDP or other neuropathies. In addition, patient responses may be influenced by unrelated health issues. In a 2002 study, the SF-36, together with 3 other measures (MRC-SS; sensory sum score; Hughes functional scale) was shown to complement traditional outcome measures in 144 patients with immune-mediated polyneuropathies, including 23 patients with CIDP.[49] The SF-36 demonstrated acceptable validity and internal consistency values and moderate to good standardized response. Patients who were more disabled had lower scores on the physical measures compared with the less disabled. In general, patients alter their functional expectations over time and learn to cope with their limitations as mental health and subjective well-being were the least affected parameters.[48] The SF-36, therefore, complements the traditional assessment of symptoms, signs, and laboratory studies in these conditions and facilitates the evaluation of not only physical but also mental functioning. Neurospecific QoL measures, such as the NeuroQoL, have been validated in other neurologic conditions but have not been widely adopted and have not been used in CIDP.[50] A new disease-specific, health-related QoL scale has recently been validated in patients with CIDP, MMN, and monoclonal Ab-associated polyneuropathy, termed the Chronic Acquired Polyneuropathy Patient-reported Index (CAP-PRI). The CAP-PRI assesses various life domains, including physical and social functioning, pain, and emotional well-being and appears to cover the various degrees of disease severity. Although not yet used in clinical trials of CIDP, the CAP-PRI is quick, easy to use and interpret, and available in the public domain and thus may be well suited for assessing QoL in clinical practice.[51]

A comprehensive examination of the relationships between impairments, activity levels, participation restriction, and reduction in QoL has been reported using the data from the ICE trial.[52] This analysis suggested that changes in strength, sensation, and some neurophysiologic measures are associated with a restriction on daily activities and social participation and a reduction in QoL. Up to two-thirds of disability was accounted for by impairment measures and half of the variance of QoL component measures was explained by a combination of impairment and activity measures. Future studies are needed to further explore the impact of CIDP on disability and QoL changes.

Practical application of outcome measures

There are no evidence-based data to guide the timing of outcome assessment in those with CIDP. Based on a large interventional trial in CIDP, it is advisable to assess CIDP outcomes at month 3 after starting treatment as most who respond to treatment should do so within the first 3 months.[7] Periodic assessments thereafter are highly influenced by individual disease severity and response to immunotherapy. Repeat clinical assessments are encouraged before and after dosing changes. It may also be preferable to arrange assessments immediately prior to IVIG to capture patients at their theoretically worst CIDP status.

Patient-related outcome measures (PROMs) are emerging as a valuable means of assessing response to IVIG therapy, and are increasingly administered in the home setting.[53] The use of PROMs is particularly appropriate in conditions such as CIDP, where disease manifestations are readily evident to the patient and may vary with daily activities.[54] The utility of home evaluation of I-RODS has been previously discussed.[16] A small study found strong correlations between clinic and home evaluations of I-RODS and INCAT scores in leg function, although INCAT scores for arm function showed significant differences, with home evaluations typically scoring 1 point less.[55] In some clinical practices, frequent patient-reported grip strength collection at home with electronic communication to the physician is utilized to complement outcomes collected during routine clinical visits. The feasibility and reliability of at-home grip strength collection has not been reported in large groups of CIDP patients. Important advantages of at-home collection include frequency of data entry, the ability to monitor remotely, and the collection of data at clinically critical time points (e.g., end-of-cycle IVIG deterioration, after-treatment assessment of response, or for relapse after therapy discontinuation).

Summary and concluding remarks

The applicability of an outcome measure is dependent on its validity, reliability, and capacity to detect meaningful clinical changes over time ("responsiveness").[56] Ease of implementation in clinical practice is also important. To be useful in a clinical setting, outcome measures need to navigate constraints in time, equipment, and expertise while also providing accurate data that inform therapeutic decisions. It is important to be aware of the possibility of misinterpretation. Uniform assessment and clinical judgment are necessary when interpreting results.

This article has highlighted advantages and disadvantages of several outcome measures for CIDP. While some have potential application during routine clinical care, several challenges remain. Although a sustained disease remission with complete or near-complete clinical recovery is achievable in some patients with CIDP, this is not the case for all. Residual irreversible deficits are not uncommon in patients with both

immunologic active and inactive disease. One challenge that often arises during CIDP treatment is separating stable immunologically inactive deficits from an ongoing or active inflammatory process. For patients with well-defined active disease another challenge is optimization of therapy, thereby avoiding the potential toxicities or accumulating disability that can come with over- and undertreatment. At present, there is no single assessment that can differentiate between active and inactive disease, or that can identify optimal treatment response. However, a combination of these assessments over time along with clinical and electrodiagnostic findings may provide a better idea of whether weakness and function have the potential for recovery. The tools that have traditionally been used during routine clinical care to guide treatment decisions are inadequate. Gathering a better understanding of a patients' disability and strength impairment over time, along with subjective patient experience and neurologic examination, can assist the clinician in dosing adjustment decision-making and, in general, optimizing treatment plan. This is especially true if those assessments of disability and strength impairment are valid and disease-specific. I-RODS and grip strength collection appear poised to fill the gaps in routine clinical monitoring of patients with CIDP. When further combined with measures of gait and fatigue, the potential to understand CIDP disease activity status and to make informed treatment decisions is enhanced. Even so, the emphasis placed on any one assessment, no matter how objective, is uncertain. There is an unmet need for a CIDP biomarker, CIDP specific immunologic signature, or composite clinical measure that can broadly assess disease activity, functional status, and the effect of therapy at different stages of the inflammatory process.

We strongly endorse the use of objective outcome measures in clinical practice. Strength impairment testing with a handheld dynamometer is a validated measure that can be collected quickly. Although the Jamar and vigorimeter devices require purchase (available online from $200–400), the cost is similar to other devices routinely used as part of the bedside neurologic examination. I-RODS, INCAT, and/or ONLS are available at no cost and take little time during a visit. Even though not validated in CIDP, a gait assessment with TUG or 10MWT can potentially provide useful data. Fatigue and pain scales can also be recorded to complement one of the above objective measures.

Additional studies are needed to develop and validate reliable outcomes measure for routine clinical assessments in CIDP. We contend that the development of a weighted composite measure, incorporating multiple assessments including patient- and physician-reported outcomes, potentially available as a mobile app and based on gaming technology is one future possibility and addresses an essential unmet need in the care of patients with CIDP.

Please see Important Safety Information about GAMUNEX-C on the following pages and refer to the brief summary of full Prescribing Information[57] in the Appendix.

Important safety information

GAMUNEX®-C (immune globulin injection [human], 10% caprylate/chromatography purified) is indicated for the treatment of primary humoral immunodeficiency disease (PIDD) in patients 2 years of age and older, idiopathic thrombocytopenic purpura (ITP), and chronic inflammatory demyelinating polyneuropathy (CIDP).

Thrombosis may occur with immune globulin products, including GAMUNEX-C. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors. For patients at risk of thrombosis, administer GAMUNEX-C at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with immune globulin intravenous (IVIG) products in predisposed patients. Patients predisposed to renal dysfunction include those with any degree of preexisting renal insufficiency, diabetes mellitus, age greater than 65, volume depletion, sepsis, paraproteinemia, or patients receiving known nephrotoxic drugs. Renal dysfunction and acute renal failure occur more commonly in patients receiving IVIG products containing sucrose. GAMUNEX-C does not contain sucrose. For patients at risk of renal dysfunction or failure, administer GAMUNEX-C at the minimum concentration available and the minimum infusion rate practicable.

GAMUNEX-C is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin. It is contraindicated in IgA-deficient patients with antibodies against IgA and history of hypersensitivity.

Severe hypersensitivity reactions may occur with IVIG products, including GAMUNEX-C. In case of hypersensitivity, discontinue GAMUNEX-C infusion immediately and institute appropriate treatment.

Monitor renal function, including blood urea nitrogen (BUN), serum creatinine, and urine output in patients at risk of developing acute renal failure.

Hyperproteinemia, increased serum viscosity, and hyponatremia may occur in patients receiving IVIG treatment, including GAMUNEX-C.

There have been reports of noncardiogenic pulmonary edema (transfusion-related acute lung injury [TRALI]), hemolytic anemia, and aseptic meningitis in patients administered with IVIG, including GAMUNEX-C.

The high-dose regimen (1g/kg x 1-2 days) is not recommended for individuals with expanded fluid volumes or where fluid volume may be a concern.

Because GAMUNEX-C is made from human blood, it may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

Do not administer GAMUNEX-C subcutaneously in patients with ITP because of the risk of hematoma formation.

Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of BUN and serum creatinine, before the initial infusion of GAMUNEX-C and at appropriate intervals thereafter.

Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies, because of the potentially increased risk of thrombosis.

If signs and/or symptoms of hemolysis are present after an infusion of GAMUNEX-C, perform appropriate laboratory testing for confirmation.

If TRALI is suspected, perform appropriate tests for the presence of antineutrophil antibodies and anti-HLA antibodies in both the product and patient's serum.

After infusion of IgG, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation.

In clinical studies, the most common adverse reactions with GAMUNEX-C were headache, fever, chills, hypertension, rash, nausea, and asthenia (in CIDP); headache, cough, injection-site reaction, nausea, pharyngitis, and urticaria with intravenous use (in PIDD) and infusion-site reactions, headache, influenza, fatigue, arthralgia, and pyrexia with subcutaneous use (in PIDD); and headache, vomiting, fever, nausea, back pain, and rash (in ITP).

The most serious adverse reactions in clinical studies were pulmonary embolism (PE) in 1 subject with a history of PE (in CIDP), an exacerbation of autoimmune pure red cell aplasia in 1 subject (in PIDD), and myocarditis in 1 subject that occurred 50 days post-study drug infusion and was not considered drug related (in ITP). ❑

Please see the brief summary of full Prescribing Information for GAMUNEX-C in the Appendix.

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