Expert Review of Neurotherapeutics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iern20

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To cite this article: Jeffrey A. Allen, Filip Eftimov & Luis Querol (2021) Outcome measures and biomarkers in chronic inflammatory demyelinating polyradiculoneuropathy: from research to clinical practice, Expert Review of Neurotherapeutics, 21:7, 805-816, DOI: 10.1080/14737175.2021.1944104

To link to this article: https://doi.org/10.1080/14737175.2021.1944104

Published online: 02 Jul 2021.

EXPERT REVIEW OF NEUROTHERAPEUTICS
2021, VOL. 21, NO. 7, 805–816
https://doi.org/10.1080/14737175.2021.1944104

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REVIEW

Outcome measures and biomarkers in chronic inflammatory demyelinating polyradiculoneuropathy: from research to clinical practice

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ABSTRACT

Introduction: Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated syndrome characterized clinically by weakness and/or numbness that evolves over 2 months or more. The heterogeneity of clinical features necessitates an individualized approach to disease monitoring that takes lessons learned from clinical trials and applies them to clinical practice.

Areas covered: This review discusses the importance of clinimetrics and biomarkers in CIDP diagnosis and disease monitoring. Highlighted are the challenges of defining responses to immunotherapy, the usefulness, and limitations of utilizing evidence-based clinical outcome measures during routine clinical care, and the evolving understanding of how diagnostic and disease activity biomarkers may reshape our treatment and disease monitoring paradigms.

Expert opinion: Although disability and impairment outcome measures are commonly used in CIDP to indicate disease status, the nonspecific nature of these metrics limits the ability to attribute a change in any given metric to a change in CIDP. This interpretive challenge may be magnified by inconsistencies in the direction of change as well as a strong placebo effect. There is a need to improve our understanding of minimally important changes in existing outcome measures as a means to personalize treatment and to better assess disease activity status with biomarker discovery.

ARTICLE HISTORY
Received 13 April 2021
Accepted 14 June 2021

KEYWORDS
Chronic inflammatory demyelinating polyradiculoneuropathy; clinical outcome measures; biomarkers; diagnosis; disease activity; disability; impairment; minimal clinically important difference

1. Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated peripheral nerve syndrome that affects 1.0 to 8.9 persons per 100,000 and has an incidence of up to 1.6 per 100,000 per year [1,2]. Although CIDP is clinically heterogeneous, the core clinical characteristic features include motor and/or sensory dysfunction that evolves over 8 weeks or more in a progressive or relapsing pattern [3–5]. While between 60% and 80% of patients develop relatively symmetric proximal and distal numbness and weakness, phenotypes with variable degrees of regional (proximal, distal, or asymmetric) or modality (motor or sensory) involvement are also recognized under the CIDP umbrella [6]. Named variants include multifocal CIDP (Lewis–Sumner syndrome, multifocal acquired demyelinating sensory and motor [MADSAM] neuropathy), distal CIDP (distal acquired demyelinating symmetric [DADS] neuropathy), sensory CIDP, and motor CIDP [4,5]. At disease onset, motor CIDP and sensory CIDP variants are estimated to each make up about 10% of all CIDP, while distal CIDP may be slightly more than 10% and asymmetric CIDP slightly less than 10% [6]. Over time, about half of all patients presenting initially with restricted phenotypes develop motor and sensory symptoms and signs that are proximal, distal, and symmetric [6].

The pathophysiology of CIDP is not fully understood but likely involves diverse mechanisms between patients or perhaps even within individual patients at different stages of the disease [7,8]. Autoantibodies have traditionally been considered central in CIDP pathophysiology given that patients frequently respond to plasma exchange and intravenous immunoglobulins. The recent description of autoimmune nodopathies, a subset of neuropathies fulfilling CIDP diagnostic criteria but with specific associated autoantibodies (anti-contactin-1 (CNTN1), anti-neurofascin-155 (NF155), anti-contactin-associated protein 1 (CASPR1) and anti-nodal neurofascin 140/186 (NF140/186)), supports this view [9,10]. However, immune effector mechanisms that play a role in CIDP also include macrophage-mediated demyelination, autoantibody-dependent damage (both complement-dependent and complement-independent) [11–14] and cytotoxic T-cell damage [15]. Although specific mechanisms may predominate in some disease variants, pathophysiological overlap is presumed considering that most patients respond to either intravenous immunoglobulins (IVIg) or corticosteroids.

The importance of early CIDP diagnosis and treatment before irreversible nerve injuries have occurred is indisputable. Equally indisputable is the fact that CIDP is misdiagnosed and overtreated [16]. This situation underscores the importance of using sound clinimetric markers of treatment response when

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Article highlights

- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare and heterogeneous immune-mediated peripheral nerve syndrome with several clinical variants.
- Since CIDP misdiagnosis and overtreatment is common, diagnostic and disease activity biomarkers are needed to improve diagnostic accuracy and guide treatment decisions.
- In clinical trials, CIDP outcome measures commonly used include metrics for disability, impairment, and quality of life.
- In clinical practice, the collection of structured outcome measures to support a diagnosis and treatment response is highly variable and frequently inadequate.
- There is an evolving understanding of the minimum clinically important difference (MCID) for outcome measures typically followed in patients with CIDP. The rigidity of MCID interpretation in clinical trials may not always be needed in clinical practice when outcomes of different domains are in agreement. Interpreting MCID becomes challenging when multiple metrics point in different directions.
- Although the quest for biomarkers that reflect the underlying pathobiology and outcomes of CIDP has been underway for more than a decade, robust biomarkers for diagnosis and disease monitoring are still lacking.
- Some areas of biomarker research include tissue status, effector mechanisms, nerve function, and drug effect.
- Ideally, a panel of CIDP biomarkers will emerge that can be utilized selectively to capture the full spectrum of CIDP diagnostic heterogeneity and facilitate disease monitoring across a wide range of clinical scenarios.
- The international registry Inflammatory Neuropathy Consortium Base (INCbase) aims to collect a standard set of clinical outcomes and biomaterials from patients across the CIDP spectrum. The study expects to uncover enlightening clinical and biological data to better define the boundaries and immunologic underpinnings of CIDP.

treatment response is used as a diagnostic test for CIDP, and highlights the need to develop diagnostic and disease activity biomarkers. Monitoring disease activity with a diverse suite of biomarkers (electrophysiology, imaging, soluble axon damage biomarkers, etc.) that reflect the diverse immunobiological underpinnings of CIDP may facilitate more targeted use of immunotherapies to maximize therapeutic benefit and avoid overtreatment. This review examines currently available metrics for CIDP disease monitoring in clinical practice and explores the state of the art of CIDP biomarker development.

2. Defining the treatment response: challenges and limitations

IVIg, corticosteroids, and plasma exchange are first-line treatment options for CIDP[17–20]. Between 80% and 90% of patients respond to one or more of these therapies [21–24]. Although no consensus exists on which first-line intervention is best, several factors restrict the use of plasma exchange to patients who are severely affected or have treatment-refractory disease. Regardless of which therapy is chosen, if a benefit is forthcoming, it should be appreciated within 3 months in most instances and probably within 6 months in all patients. Since the definition of 'benefit' strongly influences treatment duration, as well as the very diagnosis being treated, it is critically important that 'benefit' is defined as clearly and objectively as possible. This task, however, is not without challenges. There is no universal definition of what it means to be a treatment responder. While benefit may be easy to document in some patients, often it is not.

A 'test of treatment' is a strategy frequently employed during the diagnostic process for conditions that lack diagnostic biomarkers [25]. Within CIDP diagnostic guidelines, 'objective improvement following immunomodulatory treatment' is considered supportive of a CIDP diagnosis [4]. While a 'test of treatment' can be diagnostically useful when the differential diagnosis is narrow, the pretest probability is high, and there is a measurable objective outcome, problems occur when 'benefit' is loosely defined. It has been shown that 85% of patients who were misdiagnosed and treated as CIDP felt better with immunotherapy when benefit was broadly and *subjectively* defined [26]. Only rarely was there *objective* evidence of improvement in misdiagnosed patients and, in most cases, those patients were found to have immune-mediated disorders that were mismanaged as CIDP. Evidence from randomized controlled trials (RCTs) of CIDP indicates that between 30% and 40% of patients randomized to placebo are able to reduce or stop other immunotherapies while maintaining or improving disability [27–34]. These observations may reflect the normal fluctuation that occurs in CIDP as well as measurement variability with the available clinimetric scales, but also highlight the role that placebo can have on treatment response. In no study is the impact of placebo on CIDP treatment more striking than in the PATH study of subcutaneous immunoglobulin (SCIg) [34]. In this RCT, participants were required to demonstrate immunoglobulin dependency by documenting clinical deterioration after open-label IVIg withdrawal, followed by clinical improvement after open-label IVIg restabilization. Only subjects with decline and then improvement on open-label IVIg were randomized to blinded SCIg or placebo. Despite this requirement, 37% (19/51) of patients randomized to blinded *placebo* did not relapse.

The term 'placebo effect' has been used to describe the non-deterioration of patients receiving placebo [35]. Among factors likely to influence the placebo effect are 'subject expectation' in which a response to treatment is elicited based on what the subject expects to happen; and 'conditioning' in which there is a learned response to treatment after prolonged use of a medication. These factors almost certainly impact clinical practice similarly to clinical trials, and reinforce the importance of using objective outcomes if a 'test of treatment' strategy is to be employed during routine clinical care. Even then, however, treatment expectations and conditioning may impact on outcome measures in unpredictable ways. It can be difficult to ascertain whether improvement (or deterioration) is based on a change in disease pathobiology or whether the metric is instead capturing a placebo phenomenon similar to that observed in the PATH trial. It is within this ambiguous interpretive space that the need for biological markers of disease activity becomes so important.

2.1. Illustrative case 1: treatment of a naïve patient

A 41-year-old man presented with 3 years of slowly worsening paresthesia and weakness in his hands and feet as well as a mild hand tremor. On examination, deep tendon reflexes were diffusely hypoactive. Nerve conduction studies (NCS)

showed unequivocal slowing of motor nerve conduction velocity (CV) with median and ulnar CV in the low 30s m/sec and peroneal and tibial nerves motor CV in the upper 20s m/sec. A 30–50% conduction block was appreciated in the ulnar nerve forearm segment. Sensory response amplitudes were attenuated in the upper limbs and absent in the lower limbs. Cerebrospinal fluid (CSF) protein concentration was normal (49 mg/dL).

The patient fulfills the diagnostic criteria for CIDP, although he would be classified as having the 'distal CIDP' variant. Considering the many CIDP diagnostic mimics of the distal CIDP variant, genetic testing may be reasonable to pursue in this patient. If genetic testing is unavailable or inconclusive then a 'test of treatment' might be entertained. If immunotherapy is initiated, the main clinical questions are as follows: 1) how does treatment response inform conclusions about the diagnosis? 2) how does treatment response inform justification for long-term therapy?

Several outcome measures are available to objectify the treatment response in clinical practice. In this patient, grip strength and the Inflammatory Rasch-built Overall Disability Scale (I-RODS) questionnaire were chosen to monitor disease. IVIg therapy led to normalization of I-RODS scores and doubling of grip strength (Table 1). The results were diagnostically supportive of CIDP and provided justification for continued IVIg treatment.

2.2. Illustrative case 2: treatment optimization

In 2013, a 78-year-old man developed symmetric proximal and distal numbness and weakness. NCS showed an unequivocal demyelinating polyneuropathy with multiple conduction blocks. Symptoms progressed over about 6 months and, in March 2014, he began treatment with high-dose prednisone. Corticosteroids were unhelpful and, in September 2014, the patient was switched to IVIg. Treatment began with a 2 g/kg loading dose, followed by 1 g/kg maintenance therapy every 3 weeks. In 2015 and 2016, the dose and frequency of IVIg were optimized such that the patient was stable between infusions, eventually settling at a 1.2 g/kg dose every 2 weeks. Intravenous rituximab (1000 mg × 2) was administered in October 2019 followed by a single 1000 mg dose in January 2020.

There are no known CIDP biomarkers of disease activity. In this patient receiving high-dose IVIg: 1) what evidence has been gathered to justify aggressive immunoglobulin treatment? 2) is there adequate evidence that the benefits of rituximab therapy outweigh the risks?

Periodic collection of disability outcomes (e.g. I-RODS) or impairment (e.g. grip strength) can inform evidence-based decision-making in CIDP. In this case, I-RODS and grip strength measurements were well documented prior to initiation of rituximab (Table 2(a,b)). Decreasing the dose and frequency of IVIg from 1.2 g/kg every 2 weeks to 1 g/kg every 3 weeks led to a reduction in I-RODS raw scores (from 43 to 33), and reduced left-sided grip strength (from 27 to 16 kg). These metrics improved once IVIg dosing was restored to 1 g/kg every 2 weeks. A similar reduction in IVIg dose was attempted after rituximab administration but with the same result; specifically, an unequivocal deterioration of grip strength and increase in disability. In the absence of a biomarker that informs more precisely about disease activity, collecting these outcomes during routine clinical care can provide information to guide treatment decisions. In this case, the data indicated that rituximab was not beneficial and that high-dose IVIg was justified.

2.3. Illustrative case 3: treatment withdrawal

A 29-year-old man with acute onset CIDP developed proximal and distal motor and sensory deficits and areflexia over a 4-week period in November and December 2015. NCS showed unequivocal slowing of CV. CSF protein concentration was elevated (111 mg/dL). In December 2015, IVIg treatment

Table 1. Case 1: outcomes pre- and post-treatment with intravenous immunoglobulin (IVIg).

	May 2019	July 2019	August 2019	November 2019	March 2020	July 2020
I-RODS (raw)	43	41	IVIg started	47	48	48
Grip strength, right (kg)	19	12	2 gm/kg followed by 1 gm/kg q 3 weeks	44	Virtual	43
Grip strength, left (kg)	18	10		42	Virtual	40

I-RODS, Inflammatory Rasch-built Overall Disability Scale.

Table 2. Case 2: outcomes following treatment with intravenous immunoglobulin (IVIg) or rituximab.

		October 2018	February 2019	February 2019	April 2019	April 2019	June 2019
I-RODS (raw)	IVIg (1.2 g/kg q2w)	45	43	IVIg (1 g/kg q3w)	33	IVIg (1 g/kg q2w)	42
Grip strength, right (kg)		24	23	22		24	
Grip strength, left (kg)		23	27	16	22		

	October 2019	October 2019	January 2020	January 2020	March 2020	May 2020	May 2020	June 2020
I-RODS (raw)	42	Rituximab	Rituximab	43	IVIg (1 g/kg q3w)	35	IVIg (1 g/kg	41
Grip strength, right (kg)	23	(1000 mg × 2)	(1000 mg × 1)	22		24	q2w)	25
Grip strength, left (kg)	23			24		14		23

I-RODS, Inflammatory Rasch-built Overall Disability Scale.

led to near-complete symptom resolution. Relapses in February 2016 and July 2016 prompted initiation of IVIg maintenance therapy (July 2016), with dose escalation to 1 g/kg every 2 weeks in 2017. In 2018 and through 2019, neurologic examination including strength and sensation was normal apart from reduced lower limb reflexes.

Approximately 30% of patients with CIDP are able to achieve drug-free remission status at some point during their disease [36]. In part because of this, it is standard of care to periodically reduce or stop treatment in patients on chronic immunoglobulin therapy to understand treatment dependency [4]. With these considerations in mind: 1) what is the justification for high-dose IVIg in this patient? 2) are there objective data that support active immunotherapy-dependent disease?

The assumption made when treating CIDP is that changes in metrics (e.g. disability, grip strength) indirectly reflect change(s) in biological activity targeting peripheral nerves but those which cannot be measured directly. When multiple measures of different domains change in the same direction, confidence grows in the assumption that outcomes reflect improvement in neuropathy. However, changes in metrics are sometimes inconsistent or contradict the patient's subjective experience. When this occurs, it is difficult to know which metric to rely on or if any metric can be used to support the original assumption.

In Case 3, measurements for grip strength, MRC sum score, and sensory examination were stable during IVIg treatment, whereas the I-RODS disability score deteriorated and the patient's subjective experience slightly worsened (Table 3). While strength and sensory scores provide strong evidence that the neuropathy is stable and that high-dose IVIg is not needed, the importance of a change in disability or subjective patient experience as a reflection of CIDP disease activity is less clear. I-RODS scores, and even impairment outcome measures, are not specific to neuropathy and may be influenced by a multitude of other factors. Improvement in some metrics in this patient may have been due to immunotherapy, a placebo effect (expectations of ongoing benefit or conditioning), or a nonspecific benefit of IVIg therapy (i.e. IVIg having a positive biological effect on a non-CIDP disease). The features of this case emphasize the need for robust biomarkers to gain a better understanding of these complex issues.

3. CIDP outcome measures: from clinical trials to clinical practice

Clinical outcome measures employed in CIDP clinical trials include metrics for disability, impairment, symptoms, and quality of life (QoL) [37–40] (Table 4). Disability is generally used as a primary outcome measure, whereas impairment measures are often secondary outcomes. In the last few years, measures for symptoms (e.g. fatigue and pain) and QoL have increasingly been incorporated into study designs.

The last decade has seen a shift toward the use of linear rather than ordinal scales in CIDP, as differences in ordinal-scale data cannot be quantified. The development of linear scales enables collection of data more amenable to robust statistical analysis. For example, Inflammatory Neuropathy Cause and Treatment (INCAT) is an ordinal scale for arm and leg disability that is scored from 0 (no disability) to 10 (maximum disability) [29]. Because INCAT is an ordinal scale, changes at different positions of the scale (for example, a change from 1 to 2 *vs*. a change from 7 to 8) do not mean the same thing although, in practice, they are often falsely interpreted as equivalent. Conversely, I-RODS is a 24-item questionnaire that tabulates a raw I-RODS (ordinal) score of 0 (maximum disability) to 48 (no disability), which can then be translated easily to a centile scale or in logits that can be used in a linear fashion [41].

Most RCTs of CIDP conducted over the last 12 years have used disability as the primary outcome measure (Table 5) [29,30,33,34,42–46], commonly INCAT which is the preferred outcome measure of the United States Food & Drug Administration. Although the same outcome measures used in clinical trials are generally applied in routine clinical practice, the objectives, interpretation, and definitions of response differ by setting. In clinical trials, the objective is to define clinically meaningful differences between treatment groups that are indicative of the efficacy of a certain intervention. Clinical trials typically employ a rigidly defined primary outcome measure and multiple supportive secondary measures (usually impairment). In clinical practice, the goal of collecting data is to support treatment response in *individual* patients rather than groups. The practicalities of how that is achieved are much different compared with clinical trials and, too often, no formal outcomes are collected. In other instances, only loosely defined subjective measures are obtained. While the same rigidity necessary for clinical trials is not always needed (or feasible) in clinical practice, the lessons learned from clinical trials should not be lost completely. In clinical practice, smaller but consistent changes in outcomes across different scales may be regarded as clinically relevant. Clinical practice is also not bound to a single predefined measure. Clinicians may choose among several outcomes that best capture change in a given patient. While the time and cost considerations of outcomes collection in daily practice are real, they need not be disqualifying if the physician focuses on outcomes most relevant to a particular patient.

Minimal clinically important difference (MCID) is the smallest change in health status that an individual patient would identify as important. Although the concept was developed more than 30 years ago [47], the best method to define MCID remains under discussion. MCID may be derived by using an anchor-based or distribution-based approach. In the anchor-based method, an external criterion, often Patients' Global Impression of Change (PGIC), is the gold standard by which to determine clinical importance. Critics of the anchor-based approach argue: why not simply use PGIC? The distribution-based approach is based on the statistical properties of the test [48]. Critics of the distribution-based approach argue that statistical significance is per definition not the same as clinical relevance. Frequently used definitions of MCID in CIDP are summarized in Table 6.

When assessing MCID in clinical practice, it is important that outcome measures are performed properly so that results are reproducible. Even then scenarios may arise in which

Table 3. Case 3: outcomes following treatment with intravenous immunoglobulin (IVIg).

		July 2019	August 2019	October 2019	November 2019	January 2020	February 2020	April 2020	May 2020	July 2020	Condition
I-RODS (raw)	IVIg (1 g/kg q2w)	35	IVIg (1 g/kg q3w)	36	IVIg (1 g/kg q4w)	34	IVIg (0.7 g/kg q4w)	30	IVIg (0.4 g/kg q4w)	28	Worsening
Grip strength, right (kg)		57		52		59		Video		56	Stable
Grip strength, left (kg)		44		48		50		Video		49	Stable
MRC (0–60) sum score		60		60		60		Video		60	Stable
Sensory exam		Stable		Stable		Stable		Video		Stable	Stable
Subjective experience		Stable		Stable		Stable		Patient unsure		Possible decline	Worsening?

I-RODS, Inflammatory Rasch-Built Overall Disability Scale; MRC, Medical Research Council.

Table 4. Clinical outcome measures in clinical trials of CIDP [37–40].

Disability	Impairment	Symptoms	Quality of life
INCAT	Grip strength	mFSS (fatigue)*	SF-36*
ONLS	ISS	NRS (pain)*	EQ-5D (EuroQol)*
Modified Rankin Scale	6-min walk test		CAP-PRI
I-RODS*	TUG		

*Patient reported outcome measure (PROM).

CAP-PRI, Chronic Acquired Polyneuropathy Patient-Reported Index; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; EQ-5D, EuroQol- 5 Dimension; INCAT, Inflammatory Neuropathy Cause and Treatment; ONLS, Overall Neuropathy Limitation Scale; I-RODS, Inflammatory Rasch-Built Overall Disability Scale; ISS, INCAT sensory sum score; mFSS, modified Fatigue Severity Scale; NRS, Numeric Rating Scale; SF-36, 36-Item Short Form Survey; TUG, Timed 'up and go.'

Table 5. Primary outcome measures in randomized controlled trials for CIDP.

Trials	Reference	Primary outcome measure
ICE (IVIg vs placebo)	Hughes et al. 2008 [29]	INCAT
RMC (methotrexate vs placebo)	RMC Trial Group 2009 [30]	INCAT
PREDICT (dexamethasone vs prednisolone)	van Schaik et al. 2010 [42]	INCAT and Rivermead Mobility Index
IMC (IVIg vs prednisolone)	Nobile-Orazio et al. 2012 [43]	ONLS or modified Rankin score
FORCIDP (fingolimod vs placebo)	Hughes et al. 2018 [33]	INCAT
PATH (SCIg *vs* placebo)	van Schaik et al. 2018 [34]	INCAT
DRIP (different IVIg intervals)	Kuitwaard et al. 2020 [44]	Grip strength
ProCID (different IVIg intervals)	Cornblath et al. 2018 [45]	INCAT
IOC (IVIg continuation *vs* placebo)	ISRCTN Registry [46]	I-RODS

INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-Built Overall Disability Scale; IVIg, intravenous immunoglobulin; ONLS, Overall Neuropathy Limitation Scale; SCIg, subcutaneous immunoglobulin.

Table 6. Frequently used definitions of minimal clinically important difference (MCID) in CIDP.

Scale	MCID	Remarks
(adjusted) INCAT	1 point	Not a linear scale Less responsive in some patients May not capture all activities important to all patients
I-RODS	Individual SE (differs on the scale) on centile score or 4 points on the centile score	Calculation of MCID using individual standard errors (MCID ≥ ± 1.96 SE) requires an automated tool for calculation 4 points on raw score requires additional research to assess relevance Raw score (0–48) is easy to collect but less is known about the MCID May not capture all activities important to all patients
Grip strength, Martin vigorimeter	8 kPa 14 kPa	Repeated measurements are needed for consistency Not practical for patients with very weak grip
Grip strength, Jamar dynamometer	10% change (kg or lb)	Requires values averaged over at least 3 consecutive days Not practical for patients with very weak grip
MRC sum score	2–4 points	Usually a total score of 60 points (6 paired muscle groups) Poor interrater reliability Relatively unresponsive, especially to capture deterioration

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-Built Overall Disability Scale; MRC, Medical Research Council; SE, standard error.

directional changes in the measures of different domains are not in agreement. MCID may also vary from patient to patient depending on individual treatment goals [48], and MCID thresholds for improvement and deterioration of health status are not necessarily identical. These challenges, while not insignificant, should not discourage application of objective measures or utilization of MCID during routine clinical care. The reference MCID employed in clinical trials provides a context for interpreting the magnitude of change.

In order to incorporate MCID into clinical practice during a 'test of treatment,' it is essential that the MCID has a high sensitivity (captures change in patients with a real change in disease activity) and a high specificity (ensures that patients without a true change will not reach the MCID). Taking grip strength as an example, a change exceeding a MCID of 8 kPa may be interpreted as meaningful if the value is consistent and reproducible. Selecting a cutoff value lower than 8 kPa as a sign of change would likely increase sensitivity but worsen specificity. Changes less than the MCID may still be important, especially if they are reflective of other domains. It is nonetheless important to exercise caution not to overinterpret results less than the MCID especially if other metrics are not pointing in the same direction. Interpretation of outcomes with disparate directional changes requires a critical assessment of the patient's unique clinical characteristics and other intervening circumstances to understand which, if any,

outcome is meaningful. Conversely, large changes in an outcome that exceed the MCID may be discounted if they are easily explained by unrelated factors. Although no diagnostic test will ever have 100% sensitivity and specificity, further study is needed to better understand how MCID can reflect clinically meaningful changes in different patients more inclusively, under different clinical scenarios and during different stages of disease. A full understanding of the 'sensitivity' and 'specificity' of a MCID is an active area of research, although limited by the absence of gold standard disease activity biomarkers.

4. Disease activity biomarkers: current landscape and future trends

Biomarkers are measures that reflect the underlying pathobiology and outcomes of a disease but are not clinical markers [49,50]. The quest for biomarkers for monitoring disease activity in CIDP has been underway for decades. Although multiple disease activity targets have been explored – including autoantibodies, cytokines and complement proteins, Fc receptor modulators and IgG levels, pathological markers, electrophysiological and imaging measures – at present, robust biomarkers for diagnosis and disease monitoring in CIDP are lacking. The complex pathophysiology of CIDP [5] (Figure 1) suggests that multiple biomarkers to assess tissue status, effector mechanisms, functional aspects and drug efficacy may be required to fully capture its pathophysiological diversity.

4.1. Tissue status

Tissue status biomarkers are used to evaluate damage to the targeted tissue and may include imaging, skin or nerve biopsy, and serum biomarkers for axonal or myelin damage.

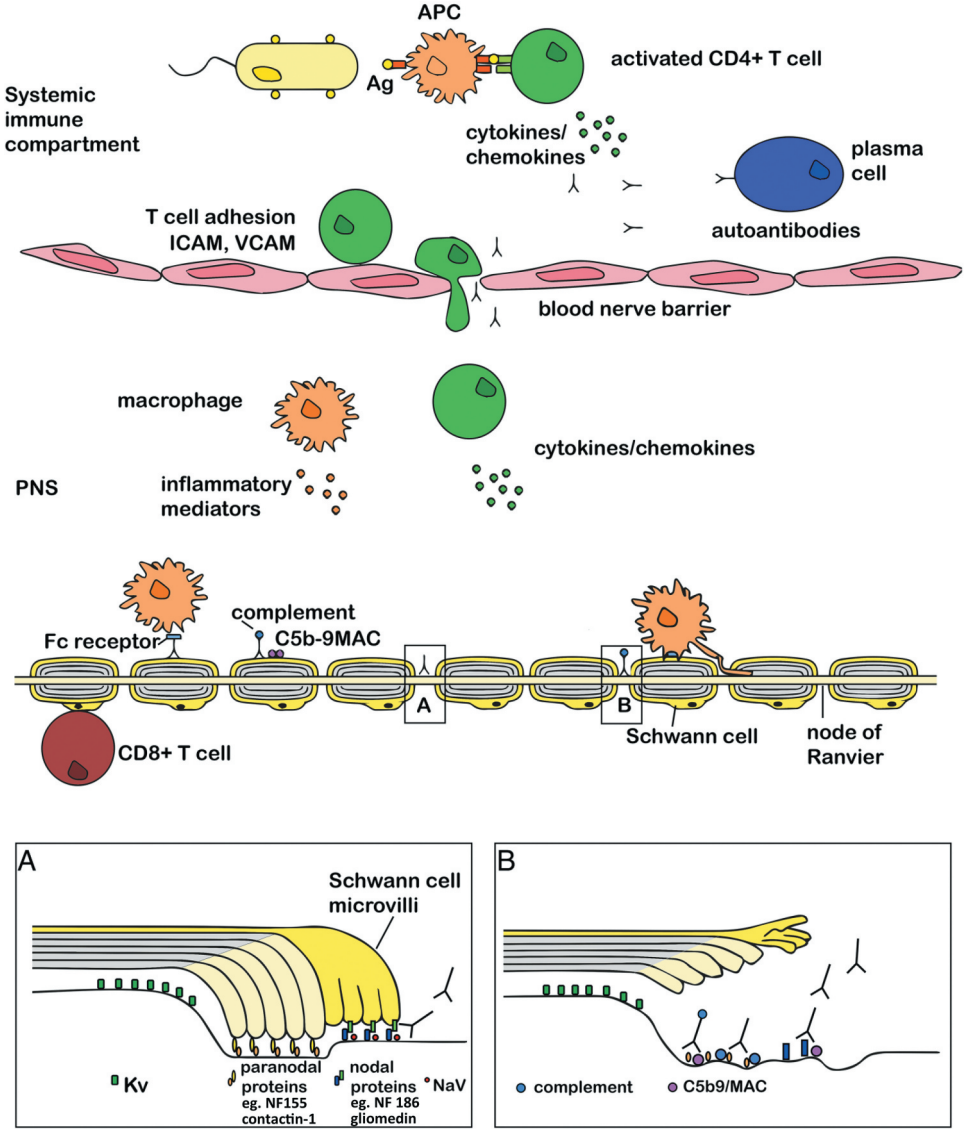

Figure 1. Immunopathology of chronic inflammatory demyelinating polyneuropathy Reproduced with permission from [5].

Inset: Effects of autoantibody binding at the node of Ranvier. (A) Interference of saltatory conduction (B) Binding of an autoantibodies followed by complement fixation and deposition of membrane attack complexes (MAC) leading to disruption or destruction of nodal and adjacent neuronal areas. Ag, antigen; APC, antigen presenting cell; C5b-9/MAC, complement terminal C5b-9/membrane attack complex; ICAM, intercellular adhesion molecules; Kv, voltage-gated K^+ channels; Nav, voltage-dependent Na^+ channels; PNS, peripheral nervous system; VCAM, vascular cell adhesion molecules.

The convenience of ultrasound makes it an attractive method of exploring tissue status in CIDP. Some authors have shown that nerve morphology on ultrasound correlates with clinical outcomes following CIDP treatment [51] and that median and ulnar nerve size normalizes or decreases in CIDP patients in remission [52]. However, at present, imaging biomarkers are more appropriate for comparing patient cohorts than for prospectively following the treatment course of individual patients. Ultrasound-based approaches require further study and should not be used at present to assess CIDP disease activity status during routine clinical care.

Although more invasive than ultrasound, skin biopsies may provide insight into CIDP tissue status. In a study of 52 patients with demyelinating neuropathies, an increased frequency of elongated nodes of Ranvier and dispersion of contactin-associated protein staining was shown in cutaneous nerves compared with axonal neuropathies ($p < 0.05$); and broadening of neurofascin staining was detectable more frequently in demyelinating neuropathies compared with normal controls ($p < 0.05$) [53]. A subsequent study of four CIDP patients who harbored high-titer autoantibodies against CNTN1 by ELISA showed paranodal anti-contactin-1 immunofluorescence labeling of dermal myelinated nerve fibers [54]. While these observations are promising, the application of skin biopsy for CIDP diagnosis or as a means to detect disease activity or treatment response requires further study and, at present, has no role during routine clinical care.

Serum neurofilament light chain (sNfL) has been explored as an axonal biomarker for several neurologic disease states, including CIDP. In a study of 29 patients starting IVIg, sNfL levels were significantly higher ($p = 0.01$) than in age-matched controls ($n = 30$), but there were no significant differences between controls and patients receiving IVIg maintenance treatment ($n = 24$) or those in long-term remission without treatment ($n = 27$). The results suggest that sNfL may be useful as a biomarker of disease activity in a subset of CIDP patients who have increased sNfL before the start of treatment [55]. Before sNFL can be widely adopted as a tissue status biomarker, prospective studies that assess axonal damage longitudinally and relative to baseline levels in the same patient are needed.

There is no known biomarker that reliably reflects myelin damage. Plasma levels of the Schwann cell-specific transmembrane protease serine 5 protein (TMPRSS5) were shown to be significantly elevated in Charcot-Marie-Tooth disease [56]; however, its role as a biomarker in acquired demyelinating neuropathies is unknown. There is some evidence that CSF sphingomyelin, a myelin-enriched lipid, may be a useful diagnostic and disease activity biomarker. Diagnostically, sensitivity (80.8%) and specificity (98.8%) in patients with acute and chronic demyelinating polyradiculoneuropathies is favorable. CSF sphingomyelin also has been shown to be higher in patients with active CIDP compared to those with stable disease and compared to axonal controls, suggesting its potential role as a disease activity biomarker [57]. Further study of CSF sphingomyelin in large cohorts of patients at various stages of disease is needed before it can be adopted into routine clinical care.

4.2. Effector mechanisms of CIDP

Effector mechanism biomarkers aim to provide insight into the pathobiological underpinnings of CIDP. The levels and activities of serum autoantibodies, as well as serum and CSF complement and cytokine profiles, may be particularly relevant [58].

Autoantibodies against proteins including the different neurofascin isoforms (NF155 and NF140/186), CNTN1, or CASPR1 have been described in approximately 10% of CIDP patients. Patients harboring these autoantibodies have diverse characteristic clinical features depending on the specific autoantibody but which include poor responsiveness to IVIg [9,59,60]. Although RCT data are lacking, numerous anecdotal reports and case series suggest that B cell depletion therapy with rituximab elicits a robust clinical response that is mirrored by a decrease in CNTN1 or NF155 autoantibody concentration [61]. In these CIDP subtypes, disease activity monitoring can potentially be assisted by autoantibody biomarkers provided that the autoantibodies can be accurately and reliably measured.

In the vast majority of patients with CIDP no pathogenic autoantibody is detected. Protein microarray studies have attempted to explore autoantibody repertoires in such patients. Although no CIDP specific antibodies have thus far been identified using this technique, in one proteomic study of about 16,000 bait proteins autoantibody profiles emerged that were able to distinguish patients by age, clinical features, and IVIG responsiveness [62]. Anchoring junction proteins were over-represented in CIDP patients. These findings provide insight into antigenic targets that require further investigation, and suggest that in some patients antigen repertoires, rather than individual specific autoantibodies, may be better suited as a diagnostic or disease activity biomarker. T-cell repertoires have also been explored in CIDP. $CD4^+$ and $CD8^+$ T cells in peripheral blood of CIDP patients receiving ($n = 11$) or not receiving ($n = 14$) IVIg revealed reduced oligoclonal expansions of both cell populations in the treatment group. The results suggested that highly activated T cells may contribute to the therapeutic effects of IVIg [63]. The results need to be confirmed in larger studies before T cell status can be used as a CIDP treatment biomarker during routine clinical care.

4.3. Nerve function

Electrophysiology provides the best surrogate biomarker of nerve function in CIDP. A *post hoc* analysis of clinical trial electrophysiological data demonstrated improvement in electrophysiologic parameters after initiation of immunotherapy [64]. Other investigators have shown that patients with worsening demyelinating abnormalities during treatment are more likely to relapse following therapy discontinuation than patients with stable or improved NCS [65]. While these findings suggest that serial electrophysiologic assessments may be useful to determine treatment response, correlation between electrophysiologic parameters and treatment outcome has not been appreciated in other groups of patients receiving chronic IVIg therapy [66,67]. An alternative functional biomarker is the

motor unit number index (MUNIX) sum score which estimates axonal loss and number of functional motor units within a nerve [68]. The MUNIX sum score was significantly lower in CIDP patients than in healthy controls ($p < 0.001$) and correlated with motor and sensory function as well as patient disability [69]. Although electrophysiological studies play an important role in CIDP diagnosis, their role in monitoring disease status is less clear. Similar to imaging biomarkers, electrophysiology biomarkers are more appropriate for comparing patient cohorts than for following the treatment course of individual patients.

4.4. Drug effect

Biomarkers for drug effect assess the mechanism of action and degree of response following treatment. Several candidates have been explored, including cytokine profiles, B cell signatures, and immunoglobulin levels. However, their value as true disease biomarkers or as biomarkers of the drug effect on the disease (and not just of the pharmacokinetics of the drug) is frequently unknown.

B cell signatures measured by flow cytometry have demonstrated reduced peripheral total B cells but markedly increased mature plasma cells in patients with CIDP ($n = 8$) and multifocal motor neuropathy ($n = 22$). Following IVIg treatment, plasma cell numbers fell rapidly, whereas B cell numbers were unchanged. The results suggested the involvement of plasma cells in the immunopathogenesis of chronic immune neuropathies including CIDP and their use as a potential biomarker for IVIg treatment response [70]. Similarly, the effect of rituximab is monitored in many diseases treated with B cell depleting therapies by analyzing CD-19^{+} B cell counts [71]. In this case, the detection of higher-than-expected B cell counts in a patient not responding adequately to rituximab could serve as a means of detecting anti-drug neutralizing antibodies. In the same setting, monitoring immunoglobulin levels could assist in detecting patients at risk of secondary immune deficiencies who are candidates for immunoglobulin replacement therapy [72].

The role of serum IgG level monitoring during IVIg treatment is unknown. Measuring serum IgG levels in 25 CIDP patients treated with individually tailored doses of IVIg showed that clinically stable patients achieved a steady-state in serum IgG levels following serial IVIg infusions [73] Although a change in serum IgG levels correlated significantly with IVIg dose ($p < 0.001$) [73], changes in immunoglobulin levels did not correlate with disease activity in a separate cohort of 25 CIDP patients receiving chronic IVIg [74] suggesting that disease activity and immunoglobulin doses depend on individual factors and that longitudinal assessment of immunoglobulin levels is not useful for disease activity monitoring or treatment needs.

4.5. Combined biomarkers

Considering the diversity of CIDP pathophysiological mechanisms and treatment regimens, it is likely that, instead of single multivalent parameters, a set of biomarkers that capture nerve integrity, nerve function, drug effect and effector mechanisms will be needed to comprehensively monitor the disease. While some biomarkers may play a larger diagnostic role to identify disease subtypes (autoantibodies, electrophysiology or imaging), others may be more useful to detect subclinical disease activity over time (sNfL) or to identify treatment failure (CD19 + B cell counts). Validation of a 'set' of biomarkers, with definitions specifying situations in which they may be useful, would facilitate the application of biomarker panels capable of addressing specific questions in unique patients at different disease stages. As an example, detection of anti-NF155 antibodies in a treatment-naïve patient helps to classify disease subtype. While the anti-NF155 antibody begins as an effector mechanism diagnostic biomarker, it also informs on the likelihood of a response to specific immunotherapies and therein guides treatment decisions. If B cell depletion therapy is administered, the antibody level along with B cell counts may be used as drug effect biomarkers and, hence, inform if and when re-treatment is needed. Collection of sNfL before and during treatment adds information about ongoing axonal degeneration as a tissue status biomarker. This set of biomarkers collectively objectifies diagnosis with effector mechanisms (autoantibodies), directs treatment (autoantibody, B cell counts), and informs on tissue status (sNfL) in a manner that is not possible with clinical outcomes alone.

5. Conclusion

Despite good clinimetric tools for CIDP, disease diversity precludes using a single metric for all patients managed in clinical practice. Outcome measures should be customized to individual patients during routine clinical care, both in terms of which outcome(s) are selected and what is regarded as the MCID. In the absence of gold standard biomarkers of diagnosis and disease activity, an important message is to diversify outcomes in order to gather complementary information across different domains.

Biomarkers are essential to improve informed decision-making. Biomarkers investigated to date are highly heterogeneous and have largely been investigated in small monocentric studies. The development and validation of new diagnostic and disease activity biomarkers is a priority in CIDP research to generate biomarker sets that, when integrated with clinical outcome measures, have the capacity to transform CIDP clinical trial design and treatment paradigms during routine clinical care.

6. Expert opinion

Our experience is that clinical outcomes collection during routine clinical care is feasible and informative when recording treatment response for patients with CIDP. In addition to assessing disability status with I-RODS or INCAT and strength impairment with grip strength, it is useful to focus also on an important task in the patient's daily life, as specific activities important to individual patients may not always be represented in disability tools. Formal assessments of gait, fatigue, pain, QoL, and a patient's overall assessment of CIDP disease activity can add another layer of information, although these measures require cautious interpretation and should not be

used as the sole basis for making treatment changes. We envision an evolving understanding of the way in which individual outcomes inform about a patient's clinical status during treatment, specifically with respect to how MCIDs from multiple measures can be used to better understand treatment response and differentiate true physiological changes from placebo responses. The best approach for addressing the placebo response in CIDP is one of active discussion. The impact of the placebo effect on CIDP clinical trials and routine clinical care is neither trivial nor benign.

Despite all efforts to objectify treatment response with clinical outcomes there are scenarios that invariably cannot be addressed by clinical measures alone. Even outcomes developed specifically for CIDP are not truly specific to that condition. INCAT and I-RODS disability scores may be influenced by a multitude of concomitant factors. Even grip strength, arguably the most straightforward CIDP metric, can be influenced by technique, pain, or effort, and thus is not entirely reliable or specific to neuropathy despite our assumptions. Biomarker discovery is poised to transform CIDP diagnostic and treatment paradigms. Although no disease activity biomarkers are currently ready for widespread use in clinical practice, intriguing candidates that require further study include sNfL, complement, and cytokine profiles, T and B cell repertoires, and autoantibodies to CNTN1 or NF155. While electrophysiology and, to a lesser extent, peripheral imaging have an undeniable role in CIDP diagnosis, their role as a tissue status biomarker of disease activity is less well defined. We envision a future in which a suite of biomarkers that can monitor tissue status, effector mechanisms, nerve function, and drug efficacy can be integrated with reliable responsive clinical outcome measures to form a new gold standard by which CIDP clinical trials are constructed and CIDP treatment decisions are made in the routine clinical care setting.

Although several investigators are currently exploring CIDP clinical outcomes and biomarkers, arguably no study will be more informative than the Inflammatory Neuropathy Consortium Base study, commonly known as INCbase (https://www.incbase.org/). INCbase is an international registry that aims to collect a standard set of clinical outcomes and biological specimens from patients with CIDP. Considering the heterogeneity of this rare disease, a worldwide collaborative effort is needed to fully capture the disease spectrum and define its phenotypic boundaries. Patients will be included at various disease stages (i.e. treatment naïve, treatment experienced, treatment remission), although those with newly diagnosed CIDP will be of greatest interest. High-quality standardized clinical data will be collected prospectively and followed longitudinally. Biomaterials will be collected at selected sites, which should aid in biomarker discovery. The study was launched in May 2020 and seeks to add participation across the globe through 2021 and beyond. It is anticipated that INCbase will help bridge the gap between clinical outcomes and biomarkers in a way not previously possible.

Acknowledgments

Editorial assistance was provided by Robert Furlong and Kerry Dechant on behalf of Content Ed Net (Madrid, Spain) with funding from Grifols SA (Barcelona Spain).

Funding

The manuscript was developed from the proceedings of a Grifols-sponsored virtual symposium, held on 28 October 2020 as part of the 2020 Peripheral Nerve Society Virtual Event.

Declaration of interest

JA Allen has received consulting fees from Argenx, Alexion, Akcea, CSL Behring, Grifols, and Takeda, speaker honorarium from Akcea and CSL Behring. F Eftimov has received grants for research in CIDP from ZonMw (a Dutch governmental agency) and Prinses Beatrix Spierfonds (Dutch Charity Funds). As principal investigator of INCbase, an international registry for CIDP, he has received grants for investigator-initiated studies within INCbase from various pharmaceutical companies. All grants were paid to his institution. He has received speakers fee from CSL Behring, Kedrion Biopharma and Grifols. Also he has received departmental honoraria for serving on scientific advisory boards of CSL Behring, UCB pharma and Takeda Pharmaceuticals. L Querol has received research grants from Instituto de Salud Carlos III Ministry of Economy and Innovation Spain, GBS CIDP Foundation International, Grifols, Novartis Pharma Spain, and Roche; has provided expert testimony to Alexion, Annexon, CSL Behring, Grifols, Merck, Novartis, Roche, Sanofi Genzyme, and UCB; serves on Clinical Trial Steering Committees for Sanofi Genzyme and UCB. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or conflict with the subject matter or materials discussed in this manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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