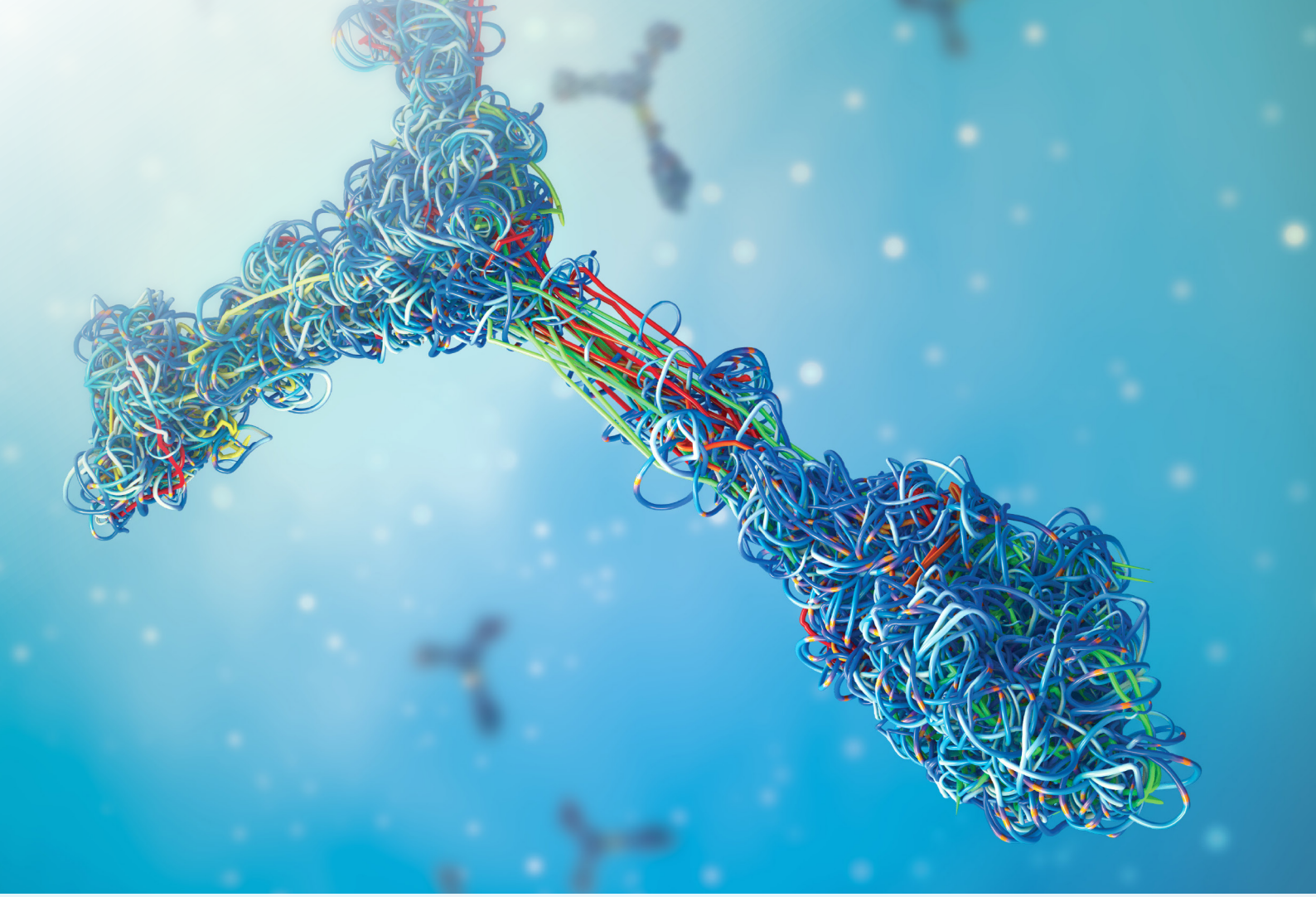

Diagnosing and treating chronic inflammatory demyelinating polyradiculoneuropathy with immunoglobulin

Indications, advice, and evidence

CLINICAL GUIDANCE ARTICLE

NATIONAL BLOOD AUTHORITY AUSTRALIA

NPS MEDICINEWISE

This clinical evidence summary has been developed as a part of the *Value in Prescribing – Immunoglobulin products* program. The program represents an evidence-based approach to fostering responsible stewardship of immunoglobulin (Ig) products, and ensure the viable and sustainable supply of Ig products in accordance with the National Policy, including the Criteria for the clinical use of immunoglobulin in Australia.

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Abbreviations

BloodSTAR: Blood System for Tracking Authorisations and Reviews

CIDP: chronic inflammatory demyelinating polyradiculoneuropathy

CMAP: compound muscle action potential

Criteria: Criteria for the Clinical use of Immunoglobulin in Australia

CSF: cerebrospinal fluid

DADS: distal acquired demyelinating symmetric

EAN/PNS: European Academy of Neurology/Peripheral Nerve Society criteria

ICER: incremental cost-effectiveness ratio

Ig: immunoglobulin

INCAT: Inflammatory Neuropathy Cause and Treatment disability score

IVIg: intravenous Ig

IVMP: intravenous methylprednisolone

LifeBlood: Australian Red Cross, Lifeblood

MADSAM: multifocal acquired demyelinating sensory and motor neuropathy

MSAC: Medical Services Advisory Committee

MRC: Medical Research Council

NBA: National Blood Authority

ONLS: Overall Neuropathy Limitations Scale

PLEX: plasma exchange

QALY: quality-adjusted life-year

SCIg: subcutaneous Ig

Overview

Key points

- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is one of the most treatable forms of polyneuropathy.
- Intravenous immunoglobulin (IVIg), corticosteroids and plasmapheresis are effective first-line treatments for CIDP.
- Objective measures of impairment and disability should be used to evaluate treatment response.
- Patients without an objective response should not continue IVIg.
- In IVIg responders, the minimal clinically effective dose should be identified by sequential, small (~20%) dose alterations.
- For patients who are clinically stable, a trial of Ig weaning towards cessation should be considered at least annually to identify patients in remission.

Chronic inflammatory demyelinating polyradiculoneuropathy (also known as chronic inflammatory demyelinating polyneuropathy, CIDP) is an acquired, relatively uncommon, inflammatory demyelinating neuropathy that affects both sensory and motor nerves and nerve roots. It is characterised by demyelination on nerve conduction studies and inflammatory demyelination on pathology. It may have a relapsing or progressive phenotype and is, in general, highly responsive to immunomodulation.

CIDP has been considered a heterogeneous disorder including a broad spectrum of clinical phenotypes. Defining subtypes remains of clinical interest as they likely differ in their pathogenesis, response to treatment and prognosis.

Epidemiological studies have demonstrated significant global variation in incidence and prevalence of CIDP. This has been largely attributed to incomplete capture, misdiagnosis of mimics, inclusion of CIDP variants and application of different diagnostic criteria, although true geographical differences as described for other autoimmune disorders have not been excluded. The most reliable estimates come from a recent meta-analysis,[1] which reported a pooled incidence of 0.33/100,000 person years and prevalence of 2.81/100,000. CIDP therefore is rare, with a prevalence of about one-50th that of multiple sclerosis. All studies have demonstrated a male predominance (gender rate ratios 1.5–4.0) with increasing incidence and prevalence with age.

However, Australian immunoglobulin (Ig) treatment data are inconsistent with global prevalence, with 2715 patients receiving Ig for CIDP in 2019 according to National Blood Authority (NBA) data. Based on the population at the time (25,549,600),[2] this gives an estimated treatment prevalence of 10.62/100,000, about four times greater than global estimates. Plausible explanations include global underdiagnosis, uniquely high Australian prevalence, or a substantial Australian overdiagnosis/misdiagnosis, with trials or continuation of Ig treatment for a range of other neuropathies.

Although the exact pathogenesis is unclear, CIDP is thought to be mediated by both cellular and humoral immune reactions directed against the peripheral nerve myelin or axon.[3] The search for neural antigen-specific autoantibodies has led to only a small percentage of cases where a known autoantibody has been found.[4] The majority of these are IgG4 antibodies directed at nodal and paranodal proteins including neurofascin and contactin. These cases may require different treatments and constitute less than 10% of cases.

Diagnosis

In the absence of a diagnostic biomarker, the diagnosis of CIDP relies on a combination of clinical, electrophysiological and laboratory features with exclusions to eliminate other disorders that may mimic CIDP. The presence of at least nine sets of diagnostic criteria demonstrates the significant difficulty that exists for many cases.

The most widely accepted diagnostic criteria are those outlined by the *European Academy of Neurology /Peripheral Nerve Society Guidelines* (EAN/PNS 2021).[5,6,7]

The EAN/PNS guidelines include clinically defined typical CIDP and CIDP variants and have well-defined electrodiagnostic and supportive criteria.

Inclusion criteria

Clinical inclusion criteria for typical CIDP

Typical CIDP is characterised by progressive, symmetric, step-wise or recurrent weakness in proximal and distal muscles of the upper and lower limbs; sensory involvement of at least two limbs, developing over at least 8 weeks; and absent or reduced tendon reflexes in all limbs. Typical CIDP accounts for at least 50% of presenting phenotypes.

Clinical inclusion criteria for CIDP variants

CIDP variants are still considered CIDP but include one of the following:

- **Distal CIDP**: distal sensory loss and muscle weakness predominantly in the lower limbs (distal acquired demyelinating symmetric [DADS]).
- **Multifocal CIDP**: sensory loss and muscle weakness in a multifocal pattern; usually asymmetric; upper limb predominant; in more than one limb (multifocal acquired demyelinating sensory and motor neuropathy [MADSAM] and Lewis–Sumner syndrome).
- **Focal CIDP**: sensory loss and muscle weakness in only one limb (eg, involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb).
- **Motor CIDP**: motor symptoms and signs without sensory involvement; if sensory nerve conduction is abnormal in apparent motor CIDP , the diagnosis is motor-predominant CIDP.
- **Sensory CIDP**: sensory symptoms and signs without motor involvement (including chronic, immune, sensory polyradiculopathy affecting the central process of the primary sensory neuron).

Note: tendon reflexes may be normal in unaffected limbs.

Over time, many of the variant presentations evolve into a more typical picture and may only represent 18% of the long-term pool of patients with CIDP. For example, long term follow-up studies have shown that sensory CIDP is often a transient clinical stage that precedes the appearance of weakness in about 70% of patients.[8]

The full list of exclusion and supportive criteria can be found in Appendix A.

Cerebrospinal fluid examination

Although cerebrospinal fluid (CSF) reveals cytoalbuminologic dissociation in 80–95% of those with typical CIDP, interpretation of what constitutes an abnormal CSF protein is limited by the lack of a universal CSF protein upper reference limit (URL).[9] The widely used URL of 0.45 g/L may be erroneously low[10,11] and incorrectly used as a supportive diagnostic criterion. When age-adjusted URLs of 0.50 g/L for patients 50 years and younger, and 0.60 g/L for patients older than 50 years are applied to CIDP, diagnostic specificity improves without a meaningful compromise in diagnostic sensitivity.[12]

Raised CSF protein concentration should be used cautiously as confirmation of diagnosis as it can also be seen in patients with diabetes mellitus, infiltrative conditions, degenerative spinal disease and Charcot–Marie–Tooth Disease/hereditary neuropathies. Indeed, the more severe hereditary demyelinating neuropathies (such as Dejerine–Sottas Syndrome) are defined by severely demyelinating conduction velocities and an elevated CSF protein.[13]

Other investigations

Tests for neuronal autoantibodies, while interesting, are not routinely available in Australia. Local or international research testing should be considered in definite cases with appropriate features.

The 2021 EAN/PNS diagnostic criteria[5] suggest use of imaging (magnetic resonance imaging [MRI] or ultrasound) to aid diagnosis in adult patients fulfilling diagnostic criteria for possible CIDP but not for CIDP. In these patients, CIDP may be more likely if MRI findings show enlargement and/or increased signal intensity of nerve root(s) on T2 weighted MRI sequences: 35–61% of patients with typical CIDP, CIDP variants, or multifocal motor neuropathy have some MRI abnormalities.[14]

Qualitative and quantitative aspects of ultrasonography have also been investigated, with ultrasound being more readily available than MRI. Currently, ultrasound and MRI are most useful as a diagnostic aid to differentiate inflammatory neuropathies, especially pure motor varieties, from other, currently untreatable conditions.

Nerve biopsies may not show clear inflammatory cell collections but only isolated endoneurial inflammatory cells. De- and re-myelination result in onion bulbs that may be seen on light microscopy as well as electron microscopy. Nerve biopsy for CIDP diagnosis should be considered only in specific circumstances.[5]

Electrodiagnostic criteria

Whilst documentation of peripheral nerve demyelination is an essential part of the CIDP diagnostic process, studies have shown that electrodiagnostic interpretive errors contribute significantly to CIDP misdiagnosis.[15] A number of common electrophysiologic patterns have been found to contribute to diagnostic errors. These include:

1. Amplitude-dependent conduction velocity (CV) slowing in length-dependent axonal neuropathies, as a consequence of fast conducting fibre loss[16] or slowly regenerating immature nerve fibres.[17]
2. Amplitude-independent conduction slowing at sites prone to compression or entrapment. This should not be considered as supportive evidence in the absence of demyelinating change in contiguous segments.
3. Amplitude-dependent and independent CV slowing in patients with diabetic neuropathy. The degree of slowing correlates with diabetic severity and duration.[18,19] Electrophysiologic differentiation from CIDP can be difficult, so correlation with the clinical phenotype (length-dependent polyneuropathy versus proximal weakness and diffuse areflexia) is essential to avoid misdiagnosis.
4. Demyelinating abnormalities that are restricted to the lower limbs, occur in only 6.4% of cases of confirmed CIDP (particularly when abnormalities are restricted to the fibular nerve to extensor digitorum brevis muscle). Obtaining conduction studies of more proximal muscles, such as tibialis anterior, and upper limbs, may clarify the amplitude-dependent relationship.[15]

Table 1. Commonly misdiagnosed electrophysiologic features

Electrophysiological pattern	Considerations	Suggestions to reduce misdiagnosis
Amplitude-dependent CV slowing in length-dependent axonal neuropathies	This occurs in patients with fast conducting fibre loss or slowly regenerating immature nerve fibres.[16]	Be aware that this is often mistaken for demyelination.
Amplitude-independent CV slowing at sites prone to compression or entrapment		Don't consider this as supportive evidence for a CIDP diagnosis unless there is also demyelinating change in contiguous segments.
Amplitude-dependent and independent CV slowing in patients with diabetic neuropathy	The degree of slowing correlates with the severity and duration of diabetes.[18,19]	Be aware that this correlates with the clinical phenotype – length-dependent polyneuropathy versus proximal weakness and diffuse areflexia. This is essential to avoid misdiagnosis.
Demyelinating abnormalities restricted to the lower limbs	This occurs in just 6.4% of confirmed CIDP cases,[15] particularly when abnormalities are restricted to between the fibular nerve to extensor digitorum brevis muscle.	Perform conduction studies of more proximal muscles, such as the tibialis anterior, and upper limbs to help clarify the amplitude-dependent relationship.[15]

CV = conduction velocity

Mimics and pitfalls in CIDP diagnosis are described in Figure 1.

Clinical Mimics of CIDP

Acquired Causes

1. Anti-MAG associated neuropathy
2. POEMS
3. Amyloidosis (hereditary or acquired)
4. Vasculitic multiple mononeuropathies
5. Diabetic neuropathy
6. Other neurological conditions (sarcoidosis, MND, other)

Hereditary Causes

7. HNPP
8. CMT1

Key Features Differentiating CIDP from Clincal Mimics

1. Presence of MGUS or IgM-MAG antibodies
2. Systemic features
3. Classically axonal neuropathy. Painful and multi-system (GIT +/- autonomic signs or symptoms)
4. Classically painful axonal neuropathy
5. Classical distal, symmetric polyneuropathy (predominantly small-fibre). Diabetic radiculoplexus neuropathies can be diffcult to distinguish from CIDP but are often painful at onset.
6. CNS involvement, or systemic features, or bulbar and respiratory involvement which are rare in CIDP.
7. History of recurrent symptoms triggered by mild trauma at compression sites.
8. Slow clinical progression. Neurophysiology shows uniform conduction velocity slowing.

Neurophysiological Pitfalls

- Electrophysiological features don't meet EAN/PNS 2021 guidelines
- Demyelinating features due to severe axonal loss
- Demyelinating features at compression sites
- Extra caution is required in interpreting NCS/EMG in the presence of diabetes

Treatment Pitfalls

- Subjective patient reported improvement in overall quality of life/fatigue/pain
- Subjective patient reported improvement in strength and/or sensory symptoms
- Reconsider diagnosis in patients apparently refractory to all three first-line therapies.
- Suggested "minimum core set" for assessing response to treatment and disease activity:
  - Impairment: Manual muscle testing (ie. MRC sum score), grip strength
  - Activity/Participation Level: R-ODS, INCAT disability score

Figure 1. Mimics and pitfalls in CIDP diagnosis

MADSAM is the most common CIDP variant and presents differently from typical CIDP, with more frequent pure upper limb onset and asymmetry. It may occur in patients receiving tumour necrosis factor-alpha antagonists.[20] There is a suggestion that motor and sensory conduction block on nerve conduction studies is more common in MADSAM than typical CIDP, and that CSF protein concentration is lower.[21] DADS neuropathy can mimic the neuropathy associated with anti-MAG (anti-myelin-associated glycoprotein) antibodies in its distal, predominantly sensory, and ataxic presentation. Pure motor and pure sensory CIDP are rarer phenotypes and the reported cases have a varying degree of sensory and motor abnormalities on neurophysiology, but symptoms are localised to one domain.

Trials of treatment

Documenting objective clinical improvement using a validated metric, rather than placing validity on equivocal subjective observations, is critical for making diagnostic and treatment decisions and is a requirement for the provision of IVIg therapy under the National Blood Agreement in Australia. In one study, 85% patients misdiagnosed with CIDP felt better with immunotherapy when benefit was broadly and subjectively defined.[22] Careful and objective determination of treatment response using both an impairment (eg, Medical Research Council [MRC] sum score) and disability score (eg, Overall Neuropathy Limitations Scale [ONLS]) is a critical practice point. Treating physicians need to be wary of patient-reported improvement in symptoms such as fatigue and pain as being the only evidence of a treatment response.

Diagnosis and misdiagnosis

Misdiagnosis of CIDP is very common, with rates of misdiagnosis in treated patients approaching 50%.[22] This may reflect a strong placebo response with the first-line therapies IVIg and steroids, difficulties in establishing the aetiology of many neuropathies that remain idiopathic, and a desire by clinicians to provide optimism for a treatable cause of neuropathy and/or concern to not miss a treatable neuropathy.

In Australia, the differential diagnoses accounting for many misdiagnoses and cases refractory to first-line therapies include hereditary demyelinating neuropathy, idiopathic axonal neuropathy, diabetic neuropathy with some slowing on neurophysiology, and pain syndromes.

Treatment of CIDP

Basis of CIDP treatment

CIDP is generally a treatable disorder with good recovery of function if marked axonal damage has not occurred. However, not all individuals will respond to a particular therapy, especially individuals with CIDP variants. Additionally, immunotherapies that may have a rapid effect on the immune system do not necessarily have an immediate effect on peripheral nerve function, and some components of PNS damage (such as axonal degeneration) may not recover well. Recovery of near-normal function should be the aim of treatment. Minimal CIDP does not necessarily require treatment[23,24] and patients without some degree of objective disability do not qualify for IVIg according to the current Criteria for the clinical use of immunoglobulin in Australia (see page 17 for more information).

The first-line treatments for CIDP are IVIg, plasma exchange (PLEX) and corticosteroids. The three first-line therapies are considered equally efficacious but with different side-effect profiles and onset of action. PLEX has largely faded as a first-line therapy, perhaps given ease of access to and administration of IVIg. This may be neglectful given a sham controlled, crossover trial of PLEX showed an 80% response rate with positive results in many endpoints.[25] A small, open label study found no significant difference in CIDP treatment outcomes between IVIg and PLEX.[26]

In a randomised controlled trial comparing IVIg and intravenous methylprednisolone (IVMP) (IMC trial)[27] both treatment groups showed significant improvement in functional outcome and quality of life over a 6-month treatment period, but more patients discontinued IVMP due to inefficacy, adverse events, or intolerance. Retrospective analysis of the extended study after a median follow-up of 42 months showed that IVMP, when efficacious and tolerated, had a significantly longer median efficacy (14 months) than IVIg (4.5 months) after therapy discontinuation ($p = 0.0126$).[28]

In the extended follow-up of the PREDICT trial, which compared daily oral prednisolone with pulsed oral dexamethasone,[29] cure or remission was observed in about 25% of all treated patients after mean follow-up of 4.5 years, with no significant difference between the two regimens.[30]

The mainstay treatments are all immunotherapies and are all either expensive and/or have the potential for side effects, and so should only be commenced following careful evaluation, diagnosis, and a treatment plan. The multiple visits and investigations may be daunting to the patient. The concept of a placebo or nonspecific response to therapeutic trials is worth broaching early, particularly given the response rate with an improved INCAT score to randomised placebo in the ICE trial was 21%[31] and corticosteroids are well recognised to have psychological effects including improved mood and energy.

The choice of first-line treatment depends on several factors:

- Is improvement or remission the goal? Early improvement is more likely with IVIg but remission is more likely with corticosteroids.
- Is the patient prone to corticosteroid side effects? A younger, physically active patient is less likely to develop steroid side effects than an older patient with medical comorbidities.
- Does the patient require a rapid onset of action due to severe disability? More rapid improvement is seen with IVIg and PLEX[5,25]
- Does cost matter? Even including the side effects, this strongly favours corticosteroids.
- PLEX is rarely considered first line but may be an option in a patient with good venous access and a local peripheral access PLEX unit.

Findings of the Medical Services Advisory Committee [MSAC] Application on Ig for CIDP,[32] and the Committee's decision, are briefly noted at the end of this paper.

An interesting consideration is whether combined IVIg and IVMP as induction treatment may provide dual benefits of a rapid response and higher rate of lasting remission without excessive side effects, as published in the OPTIC pilot trial.[33] This is being further investigated in a multicentre randomised controlled trial.[34]

It is uncertain if IVIg increases the likelihood of lasting remission above that of natural history. The methotrexate in CIDP study (RMC trial) showed that 44% of patients were able to reduce IVIg or prednisone without relapse.[35] This was confirmed in the FORCIDP trial, which showed that only 58% of patients withdrawn from chronic therapy with IVIg or corticosteroids had any deterioration over approximately 2 years, and only 24% of those receiving IVIg which was stopped abruptly had a deterioration within 45 days.[36] These findings suggest that misdiagnosis and remission of CIDP on any therapy (or both) are common. In other diseases, such as myasthenia gravis, IVIg provides short-term benefit but does not affect the natural history, and it is reasonable to assume the same applies for CIDP.[37] Standard medical practice for CIDP includes regular attempts to reduce the dose of, or withdraw from, ongoing treatment with IVIg or corticosteroids, to assess whether treatment is still necessary or if the patient has reached remission.[36]

The issue of what to do in the event of failure of the two first-line therapies is problematic. Re-evaluation of the diagnosis is a very important component and referral to a CIDP specialist should be considered. Patients may respond to PLEX but not other therapies; such patients may be more likely to have a peripheral nerve antibody, but these tests are not readily available. Patients who respond to corticosteroids but cannot be weaned may benefit from a steroid-sparing agent such as azathioprine or mycophenolate, which have not been the subject of randomised controlled trials in CIDP. Trials of methotrexate and fingolimod in CIDP were convincingly negative.[35,36] Higher-risk salvage therapies such as rituximab, cyclophosphamide, cyclosporine, alemtuzumab and autologous bone marrow transplantation have all been deployed in highly selected patients but are beyond the bounds of this review.

IVIg protocols

Biomarkers for treatment response and disease activity would be very useful to guide treatment. However, there are currently no biomarkers to predict disease activity and to avoid over- as well as under-treatment in CIDP.[38] Therefore, the optimum dosage and frequency of maintenance IVIg must be individually established for every patient with CIDP.[39,40]

Regardless of the choice of therapy, treatment can be considered as a two-step process: induction aimed at achieving maximal recovery and functional ability, and maintenance treatment to prevent deterioration in patients with ongoing active disease.

Initial treatment

In current practice, the initial IVIg loading dose is 2 g/kg of body weight divided over 3–5 days, depending on the patient's age and comorbidities. In many patients with typical CIDP, this is usually sufficient to determine whether the patient is responsive to IVIg.[38,41] In some patients, however, more than one treatment course is required to identify clear objective clinical improvement. There is no consensus about the optimal maintenance infusion protocol following induction, although an approach which aims for early identification of IVIg responders is optimal. Given the results of the ICE study,[31] and the requirement in the current NBA Criteria[42] to identify IVIg response by at least 4 months post-induction, subsequent infusions of 1 g/kg over 1–2 days at 3-weekly intervals are often used. In IVIg treatment responders, at least some improvement of disability can almost always be measured within 6 weeks.[43] In the ProCID trial,[44] 62% of IVIg responders showed an improvement of ≥ 1 adjusted INCAT score point after the induction dose alone (by Week 3), and nearly all patients who responded to IVIg did so within the first 6–8 weeks (a single induction dose and two maintenance doses). If no objective improvement is documented, IVIg should be ceased at this stage. If patients deteriorate prior to 4 months, IVIg should be ceased and another first-line therapy instituted.

Maintenance treatment

Once clinically stable, IVIg dose should be tapered to find the minimal clinically effective dose. The maintenance dose is reduced by 20% per course until relapse or wear-off emerges. This has been found in clinical practice to be more effective than interval lengthening with stable dosing.[45,46] Tapering IVIg has the advantage of identifying the lowest maintenance dose necessary to keep a patient stable if they prove to be IVIg dependent.[39] A minimal degree of wear-off, without impact on disability, does not necessarily require treatment modification, and provides assurance that treatment is needed and not over-utilised.[46]

IVIg dependency should be proven on a regular basis, particularly in patients with no treatment-related fluctuations. Dose reduction (for example, by 20% per course, every 6 months) should be considered to avoid over treatment[47] with consideration of a trial of weaning every 12 months in stable patients as per the NBA Criteria.[42] This is not required for patients who have significant treatment-related fluctuations over the IVIg cycle and objective deterioration at the end of the treatment cycle.

Tapering IVIg and identifying the lowest effective dose requires the treating team to be responsive and contactable to assess any potential deterioration promptly and either respond by changing dose or monitoring and reassuring the patient.

Subcutaneous immunoglobulin

Subcutaneous immunoglobulin (SCIg) has been demonstrated to be effective therapy for CIDP versus placebo.[48] The higher dose of 0.4 g/kg/wk is higher than the typical 1 g/kg/3wk protocol for high-dose IVIg. There are several reasons for considering the subcutaneous (SC) rather than intravenous (IV) route for IgG therapy in CIDP. These include decreased systemic adverse events with SC compared with IV administration; minimising 'wear-off effects' in strength and functional ability toward the end of the IV dosing intervals; convenience and quality of life preferences associated with SCIg; and difficulty with venous access associated with long-term IV administration and in paediatric patients.[49]

Although there has not been a head-to-head trial of IVIg versus SCIg, a formal meta-analysis of 138 patients with immune-mediated neuropathies (88 with CIDP) demonstrated no difference in efficacy between IVIg and SCIg but a 28% reduction in moderate and/or systemic adverse events with SCIg.[50] Patients who have been demonstrated to be IVIg responders on objective outcome scores, and stabilised for at least 3 months, should be considered for transition to SCIg.

The first SC infusion is given 1 week following the last IV infusion, with a 1:1 monthly dose conversion, divided into doses administered on 1–2 consecutive days per week. For example, a 70 kg patient receiving 1 g/kg IV every 3 weeks, would receive 24 g weekly SC over 1–2 days per week (dose rounded to full vial size). SCIg is not currently available for induction. The same validated outcome scores (adjusted INCAT/ONLS, MRC sum score) are used to monitor the progress of patients on SCIg and to downtitrate to the minimum effective dose. There is currently no data to guide trials of weaning, although a 20% reduction in monthly dose per course, similar to IVIg, is reasonable.

Whether or not SCIg is appropriate for an individual patient will depend on several factors including total monthly dose, ability to self-administer the medication, treatment plan compliance, and patient choice.

Corticosteroid protocols

Corticosteroids are widely available. There are several corticosteroid protocols in use for CIDP, with one study comparing daily prednisolone, pulsed dexamethasone and pulsed IVMP suggesting no differences in efficacy and safety.[51] Corticosteroids are much more widely available than IVIg, and are cheaper and easier to use.[52]

However, the concern around the real side effects of corticosteroids may have pushed some healthcare systems, including Australia's, to primarily use IVIg for CIDP. Several protocols and small trials have used pulsed IV or oral corticosteroids on the basis that this may reduce overall corticosteroid side effects and/or increase remission response rates, although neither safety benefit nor efficacy change was shown in a small comparative trial.[29]

Corticosteroids for CIDP are generally administered for up to 6 months as follows:

- Daily prednisone at 0.5–1 mg/kg/day (eg, 60 mg/day tapering to 0 over 32 weeks).[29]
- Second daily prednisone weaning from 120 mg every second day to 0 over 12 weeks.[53]
- 40 mg dexamethasone daily for 4 days every month.[29]
- 1 g of IV methylprednisolone every 3 weeks.[33]

Interestingly, given the widely different published protocols, the authors mainly use IVMP 1 g every 3–4 weeks, or 1g of oral prednisolone monthly.

Assessing treatment response

Disease course

The surprising lack of deterioration seen in patients randomised to placebo arms in therapeutic trials, even in those with an IgG dependency test period,[48] emphasise the clinical necessity of understanding the natural history and prognosis of patients with typical and variant CIDP. The remission rates vary between 18% in the short term (less than 6 months) to around 30% in studies with more than 5 years of data. One small study, which included patients diagnosed from 1985 to 2006, reported over 50% of patients had been stable off treatment for 4—14 years, after being treated for 0.1—22 years.[54] This is higher than many other reports and may relate to the evolution of diagnostic criteria and methods over the decades. Consequently, vigilance about disease activity needs to be sustained throughout the maintenance phase of management of patients with CIDP.

Assessing treatment response

Clinical assessment remains the most reliable way to assess disease activity and response to treatment in CIDP. Whilst patients with CIDP variants are less likely to achieve remission, no other patient, disease, investigational or treatment-related factors confer a greater chance of disease remission.[55] Individualised regimens based on clinical response post-induction, incremental decrease in dose, and/or prolongation of inter-dose interval are required.

Outcome measures

For an outcome measure to be useful both in practice and clinical trials, it must have good reliability and validity, be responsive to change, and have clinical meaning.[9] Assessing a combination of strength impairment (eg, MRCs, grip strength) and disability (eg, INCAT-ONLS, IRODS) is sufficiently quick and easy for use in routine clinical practice. Other parameters, including quality of life measures and patient global assessment of change, may also be helpful.

While electrophysiologic studies and imaging with ultrasound or MRI can provide diagnostic data, they are less practical and not validated as longitudinal assessment tools.[9] There is conflicting evidence of their use in monitoring disease activity.

Neurophysiological measures have been studied extensively as biomarkers in CIDP, in order to determine the number of nerves that need to be studied to confirm diagnosis, to predict response to treatment, and as a proxy for treatment efficacy. As an outcome measure, improvement in compound muscle action potential (CMAP) amplitudes correlates with clinical improvement but no electrophysiological outcome is suitable as a mainstream biomarker independent of clinical outcome.[56]

Patient expectations and goals

Patients will be relieved to hear upon diagnosis that this is a treatable disorder, but there are complexities in the available treatments, benefits, placebo responses and side effects, as well as occasional residual diagnostic uncertainty. In practical terms, following diagnosis, a plan for a trial of therapy or therapies should be agreed:

- What constitutes benefit from the trial should be agreed, with objective endpoints including the ONLS score, not just 'I think I feel better'.
- Additional measures meaningful to the particular patient – for instance robust restoration of ability to perform a particular task relevant to that patient, or range of gait on a 6-minute walk. These can help in the context of uncertain responses.
- The duration of a treatment trial and time to expected benefit should be agreed. IVIg and PLEX generally produce benefit well within 12 weeks, so for IVIg, a 4-month initial trial is made available to allow for clinic availability. Corticosteroids are generally trialled for a similar period but may require 6 months for full effect.

Second-line treatment should be considered early. If a response to corticosteroids is seen but not maintained on attempted weaning, multi-therapy with a steroid-sparing drug may be considered.

Potential review of the diagnosis should be discussed at the time of first diagnosis, particularly given an objective response to a treatment trial is a diagnostic test, so logically, failure to respond may suggest an alternative diagnosis or at least a review. This should not come as a surprise to the patient. There are potentially perverse disincentives to trials of withdrawal of therapies. A weaning protocol needs organisation, more frequent clinical evaluation, and potential testing (often with paid consultations) – this being in addition to any potential clinical worsening. It is reassuring that improvement upon reintroduction is expected in almost all patients from any deterioration that follows even an abrupt withdrawal of IVIg.[57]

Application and rationale for criteria for clinical use of Ig in Australia

In Australia, Ig products, like other blood products, are supplied at no direct cost to eligible patients under the National Blood Agreement (the Agreement),[58] and are managed by the National Blood Authority (NBA). The Agreement's primary objectives are:

- to provide an adequate, safe, secure, and affordable supply of blood products, blood-related products and blood-related services in Australia; and
- to promote safe, high-quality management and use of blood products, blood-related products and blood-related services in Australia.

Under the Agreement and related national blood arrangements, the NBA manages contracts with domestic and international suppliers of Ig to ensure demand for supply is met and manages a contract with the Australian Red Cross Lifeblood (Lifeblood) to collect blood and blood plasma from voluntary donors to support production and manufacture of Ig products for supply in Australia.

As collecting, manufacturing, and distributing Ig products is particularly expensive, and there is a limited supply, the NBA has a dedicated Ig Governance Program to manage Ig access, ensuring it is available for those who need it most. All healthcare professionals directly involved in the prescription, use and management of Ig have defined roles and obligations to ensure that Ig products are properly used and managed in line with the nationally agreed rules and obligations. Details are set out in The National Policy: Access to Government-Funded Immunoglobulin Products in Australia.

Rules governing patient eligibility for Ig funded under national blood arrangements are set out in the Criteria for the clinical use of immunoglobulin in Australia (Criteria). The Criteria are evidence-based and are developed and maintained by a national panel of health experts, in collaboration with federal, state and territory governments. They clearly articulate the medical conditions and circumstances for which the use of Ig funded under national blood arrangements is permitted, based on clinical appropriateness and the availability of safe, effective, and cost-effective alternative treatments.

To access Ig under the Agreement, medical officers are required to submit an authorisation request through the national online system BloodSTAR, accessed through the NBA's online BloodPortal. The system is used to manage the authorisation request and review process and ensures that access to Ig products is consistent with the National Policy. Lifeblood is contracted by the NBA to review and authorise applications and provide advice on eligibility as required.

Patients that are ineligible to access Ig products under the Criteria may be able to access Ig through a Jurisdictional Direct Order at a cost to the approved health provider, or directly from suppliers at a personal cost.

Further information is available on the NBA's website at, https://www.blood.gov.au/Ig with online training courses available through BloodSafe eLearning at: https://learn.bloodsafelearning.org.au/categories#immunoglobulin-courses.

The Criteria have standardised qualifying criteria, dosing controls, and length of authorisations, with defined clinical outcomes for access to continuing therapy. Validated outcome scores are required to determine Ig responsiveness at initial review post-induction, and at continuing review to ensure that ongoing treatment is indicated and that the patient is not in remission.

For the purposes of access to funded Ig product, the diagnosis and initial review of CIDP is limited to neurologists. Diagnosis should be based on EAN/PNS criteria.[5,6,7] Ig treatment may be prescribed for a patient in whom walking is compromised or there is significant disability, measured by an ONLS > 1.

The induction dose is set as 2 g/kg, with maintenance therapy set as 0.4–1 g/kg 2–6 weekly for IVIg and 0.2–0.5 g/kg weekly for SCIg. Maintenance treatment is usually begun at 1 g/kg 3 weekly for IVIg or 0.3 g/kg weekly for SCIg. This treatment has been shown to be effective in randomised controlled trials in CIDP over 24 weeks[31] and in an open-label study up to 52 weeks.[59] Determination of responder status should be performed at or prior to the 4-month review, based on a decrease in adjusted ONLS of at least one point, or increase in MRC sum score by at least three points. The efficacy of IVIg can usually be determined quickly after infusion, most often within 1–2 weeks after induction, particularly in patients with typical CIDP.[38] Data extracted from the ICE trial has shown that among IVIg responders, 47% patients had improved by week 3 (ie, after induction) and the remaining 53% of patients improved at week 6 after a second infusion.[43] Data from the ProCID trial has also confirmed a rapid response in the majority of patients: 62% by week 3 post induction and nearly all patients by weeks 6–8.[44]

Approximately 30% patients can be expected to be IVIg non-responders, so it is of paramount importance to cease treatment in patients who fail to show improvement in validated outcome scores at 4 months. It is also important to note that about 15% of patients with CIDP only require one or two courses of IVIg to achieve a sustained improvement,[38] so patients should not automatically be commenced on maintenance treatment if maximal recovery has been attained.

If the patient is a responder and continuing Ig treatment is considered appropriate, the maintenance dose should be downtitrated to the minimal clinically effective dose. This is usually achieved by decreasing the dose by 20% per treatment cycle, at the same inter-dose interval, until objective deterioration. The dose is then increased back to the last effective dose. IVIg dependency should be proven on a regular basis via dose reduction to avoid overtreatment.[38,47] Three large prospective studies suggested that 15–55% of patients receive unnecessary treatment during a limited follow-up period of at least 6 months.[31,35,60]

A trial of weaning towards cessation of Ig therapy should be planned for patients who are clinically stable at 12 months to identify those in remission. This may not be appropriate if the patient's disability has not stabilised, or the patient is still experiencing objective end-of-dose deterioration. If a patient has relapsed in the first 6 months of a trial off therapy, an option to recommence treatment is available. A further trial off treatment might be considered after at least 2 years.

Good practice points

- Ig treatment may be prescribed for a patient in whom walking is compromised or there is significant disability, measured by an ONLS > 1.
- Determination of responder status should be performed at or prior to the 4-month review, based on a decrease in *adjusted* ONLS of at least one point, or increase in MRC sum score by at least three points.
- Non-responders at 4 months post induction should cease IVIg.
- In responders, identify the minimal clinically effective dose for maintenance treatment.
- A trial of weaning towards cessation of Ig therapy should be planned for patients who are clinically stable at 12 months to identify those patients in remission.

MSAC review of Ig for CIDP

The MSAC application and review (#1564) examined the evidence for the use of Ig for the management of CIDP as part of the Health Technology Assessment Reviews of Immunoglobulin use in Australia.[32] A cost-utility analysis was undertaken to determine the value of Ig against corticosteroids, using a stepped care approach. The model assumed a base case of 497 g of Ig per patient per year, on average, at a cost of $60.41 per gram. Modelling generated a 10-year incremental cost-effectiveness ratio (ICER) of $197,472 per quality-adjusted life-year (QALY), and a 6-month ICER of $269,038 per QALY when comparing Ig to corticosteroids. Assumptions about the utility gain associated with Ig use, the amount of Ig used, and the price paid for Ig were key drivers of the model results.

MSAC deferred giving advice on the clinical and cost-effectiveness of Ig in the treatment of CIDP because of the substantial uncertainties identified in the submission.

The updated submission also highlighted the uncertainty of the economic analysis due to underlying uncertainty of the model inputs (effectiveness and safety data for immunoglobulin and comparators).[61] Although the new model allowed for treatment stopping and withdrawal to incorporate additional safety evidence for corticosteroids and PLEX, the findings were similar to the previous model. However, incorporation of severe and long-term adverse events associated with corticosteroids lowered the base case ICER to $116,088 per QALY for Ig versus corticosteroids.

This clinical evidence summary outlines existing evidence on the use of immunoglobulin for CIDP. This summary is not intended to be exhaustive and should not replace clinical judgement.

Additional resources

- NPS MedicineWise: www.nps.org.au/immunoglobulins
- Free online immunoglobulin education courses are available based on the requirements and stewardship principles and can be found at BloodSafe eLearning: https://learn.bloodsafelearning.org.au/categories#immunoglobulin-courses
- The NBA summarises a series of tools that may be used to assess medical conditions in patients seeking Ig treatment: https://www.criteria.blood.gov.au/NeurologicalScales
- Neurology conditions assessment methods: https://www.blood.gov.au/system/files/Neurology-Assessment-Methods-for-the-Ig-Governance-public-page-2.pdf

Appendix A

Electrodiagnostic criteria

The EAN/PNS guidelines strongly recommend nerve conduction studies to support the clinical diagnosis of CIDP and CIDP variants.[5] The electrodiagnostic criteria are summarised in Table 2 and 3 below.

Table 2: Motor nerve conduction criteria[5]

Strongly supportive of demyelination

At least one of the following:

a. Motor distal latency prolongation ≥ 50% above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or

b. Reduction of motor conduction velocity ≥ 30% below LLN in two nerves; or

c. Prolongation of F-wave latency ≥ 20% above ULN in two nerves (≥ 50% if amplitude of distal negative peak CMAP < 80% of LLN), or

d. Absence of F-waves in two nerves (if these nerves have distal negative peak CMAP amplitudes ≥ 20% of LLN) + ≥ 1 other demyelinating parameter* in ≥ 1 other nerve, or

e. Motor conduction block: ≥ 30% reduction of the proximal relative to distal negative peak CMAP amplitude, excluding the tibial nerve, and distal negative peak CMAP amplitude ≥ 20% of LLN in two nerves; or in one nerve + ≥ 1 other demyelinating parameter* except absence of F-waves in ≥ 1 other nerve, or

f. Abnormal temporal dispersion; > 30% duration increase between the proximal and distal negative peak CMAP (at least 100% in the tibial nerve) in ≥ two nerves, or

g. Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) prolongation in ≥ 1 nerve† + ≥ 1 other demyelinating parameter* in ≥ 1 other nerve.

- (LFF 2 Hz) median > 8.4 ms, ulnar > 9.6 ms, peroneal > 8.8 ms, tibial > 9.2 ms
- (LFF 5 Hz) median > 8.0 ms, ulnar > 8.6 ms, peroneal > 8.5 ms, tibial > 8.3 ms
- (LFF 10 Hz) median > 7.8 ms, ulnar > 8.5 ms, peroneal > 8.3 ms, tibial > 8.2 ms
- (LFF 20 Hz) median > 7.4 ms, ulnar > 7.8 ms, peroneal > 8.1 ms, tibial > 8.0 ms

(1) Weakly supportive of demyelination

a. As in (1) but in only one nerve

Note: To apply these criteria, the median, ulnar (stimulated below the elbow), peroneal (stimulated below the fibular head), and tibial nerves on one side are tested. If the criteria are not fulfilled, the same nerves are tested on the other side, and/or the ulnar and median nerves are stimulated at the axilla and at Erb's point. Motor conduction block or slowing is not considered in the ulnar nerve across the elbow or the peroneal nerve across the knee. Skin temperature should be maintained to at least 33°C at the palm and 30°C at the external malleolus. Frequency filter bandpass of 2 Hz to 10 kHz for all parameters except distal CMAP duration.

* Any nerve meeting any of the criteria (a-g)

† Mitsuma et al.[62]

CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CMAP = compound muscle action potentials; LFF = low frequency filter; LLN = lower limit of normal; SNAP = sensory nerve action potential; ULN = upper limit of normal

Table 3: Sensory nerve conduction criteria[5]

(1) CIDP

- Sensory conduction abnormalities (prolonged distal latency, or reduced SNAP amplitude, or slowed conduction velocity outside of normal limits) in two nerves.

(2) Possible CIDP

- As in (1) but in only one nerve.
- Sensory CIDP with normal motor nerve conduction studies needs to fulfil a. or b:
  a. sensory nerve conduction velocity < 80% of LLN (for SNAP amplitude > 80% of LLN) or < 70% of LLN (for SNAP amplitude < 80% of LLN)[63] in at least two nerves (median, ulnar, radial, sural nerve), or
  a. sural sparing pattern (abnormal median or radial sensory nerve action potential [SNAP] with normal sural nerve SNAP) (excluding carpal tunnel syndrome)[64,65,66]

Note 1: Skin temperature should be maintained to at least 33°C at the palm and 30°C at the external malleolus. Since these criteria do not permit to identify normal reference values compatible with sensory nerve demyelination, sensory CIDP cannot be more than a possible diagnosis as based on clinical and electrophysiological criteria.

Note 2: Decline in sural nerve action potential amplitude occurs with age and use of age-dependent reference values after age 60 is advised.[67]

CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; LLN = lower limit of normal; SNAP = sensory nerve action potential.

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