An approach to assessing immunoglobulin dependence in chronic inflammatory demyelinating polyneuropathy

Mahima Kapoor1,2 | Laura Compton1 | Alex Rossor1 | Elsbeth Hutton2 | Hadi Manji1 | Mike Lunn1 | Mary Reilly1 | Aisling Carr1

1Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, UK
2Department of Neurosciences, Central Clinical School, Monash University, The Alfred Centre, Level 6, Melbourne, Australia

Correspondence
Dr Aisling Carr, Centre for Neuromuscular Diseases, National Hospital of Neurology and Neurosurgery, 8-11 Queen Square, London, UK.
Email: aisling.carr@nhs.net

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Abstract
Regular immunoglobulin treatment maintains strength and prevents disability in chronic inflammatory demyelinating polyneuropathy (CIDP). Discrimination between active disease, with optimum symptom control on treatment, and disease in remission not requiring treatment is essential for therapeutic decision-making and clinical trial design. To compare treatment cessation versus gradual dose reduction in assessment of disease activity (immunoglobulin dependence) in a cohort of stable CIDP patients on maintenance immunoglobulin treatment. An approach to restabilization of immunoglobulin-dependent individuals is also described. Retrospective review of IVlg cessation or gradual reduction in 33 patients with stable CIDP on maintenance IVlg. Demographic, clinical and treatment data were collected; clinical monitoring data were recorded prospectively as part of routine clinical practice. A total of 21/33 patients (62.6%) were immunoglobulin dependent, (gradual dose reduction:11, cessation:10). Mean change in Inflammatory Rasch-built Overall Disability Scale (I-RODS) (−15, standard deviation [SD] 16) and Medical Research Council Sum Score (MRC-SS) (−4, SD: 4) was clinically and statistically meaningful (>75% exceeded minimum clinically important differences). Mean time to deterioration was 5.0 (SD: 4.6) months, shorter in cessation group (3.5 months) than gradual reduction group (8.8 months). All patients were restabilized to previous baseline (M: 2.3, SD: 4.3 months), half within 1 week of retreatment. A total of 12 patients (37.4%) remained stable without treatment for ≥2 years (remission). A total of 50% were identified rapidly by cessation and 50% by gradual dose reduction requiring mean 4.8 (SD: 2.8) years follow-up and costing £113 623 per person Ig spend. No predictors of disease activity were identified. A treatment cessation trial with close clinical monitoring is an efficient, cost-effective and safe approach to assessing disease activity in CIDP.

KEYWORDS
chronic inflammatory demyelinating polyneuropathy, dependence, disease activity, immunoglobulin, remission

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Chronic inflammatory demyelinating polyneuropathy (CIDP) comprises a group of immune-mediated disorders responsive to therapy with randomized control trial (RCT) evidence supporting efficacy of corticosteroids, plasma exchange and intravenous immunoglobulin (IVIg).1,2 If untreated, these diseases run a progressive, relapsing-remitting or monophasic course and can substantially limit patients’ activity and participation, with decreased quality of life.3 Remission can occur, but approximately two-thirds of patients remain treatment dependent in the long term.4

In clinical practice, it is important to identify those individuals who no longer need maintenance Ig treatment to remove the potential for serious Ig-related adverse events, such as thromboembolism, and reduce waste of an expensive product with limited supply.5,6 In research, particularly in the setting of therapeutic trials, participants with active (Ig-dependent) disease are essential to avoid inflation of the placebo effect. A meta-analysis of RCTs in CIDP revealed a 48% placebo effect when the primary endpoint was relapse or clinical deterioration and 11% placebo response when the primary endpoint was an improvement. Although some of this may be explained by patient expectation and conditioning, the sensitivity of outcome measures and incorrect identification of Ig-dependency likely plays a role.7

There is consensus opinion in CIDP treatment that close clinical monitoring with validated outcome measures should guide Ig dosing and frequency of maintenance Ig treatment.8,9 Recent improvements in outcome measure clinimetrics with the establishment of minimum clinically important differences (MCID) for Inflammatory Rasch-built Overall Disability Scale (I-RODS) and grip strength provide measurement thresholds on which clinical decisions can be made. However, random variation between repeated measures can occur in stable disease, and the threshold for clinical relevance may vary depending on the baseline level of disability.7 In the United Kingdom, national guidelines recommend the use of a combination of three validated disease-specific outcome measures in the assessment of Ig response.10 The output measures recommended by UK national guidelines are: Medical Research Council Sum Score (MRC-SS, maximum score = 70), Inflammatory Neuropathy Caused and Treatment (INCAT) sensory sum score, Overall Neuropathy Limitation Score (ONLS), hand dynamometry, I-RODS, 10-m walk, up and go 10 m walk and Berg Balance scale.10 Intermittent assessment for Ig dependence is advocated, but there is no consensus approach with most clinicians monitoring for clinical change alongside gradual reduction of dose or infusion frequency. Understandably, the approach taken may depend on patient-related factors such as anxiety regarding destabilization of disease upon changing treatment regimen.

Here, we examined differing approaches to assessment of Ig dependence/disease activity in clinically stable patients on maintenance Ig therapy for CIDP in one specialist centre over a 10-year period. We explored the impact on clinical scores and time to decision with sudden treatment cessation vs gradual dose titration. The re-stabilization of Ig-dependent individuals is also described.

2 | METHODS

We identified all patients with definite or possible diagnosis of CIDP according to the European Federation of Neurological Societies/Peripheral Nervous System guidelines in whom a formal assessment of Ig dependence was performed in the last 10 years.8 Here, we present data on demographics, disease duration, clinical and neurophysiological information, Ig maintenance regimen, with baseline and follow-up outcome measures in response to Ig dependence challenge. Ig dependence was tested either by gradual dose reduction or immediate treatment cessation. All data were prospectively recorded as per routine departmental practice by the peripheral nerve specialist consultant team at the National Hospital of Neurology and Neurosurgery (NHNN), London.

The MRC-SS has been consistently used throughout this period, as well as subjective patient reported peri-dose fluctuation. The I-RODS was routinely used from 2013. MCID values for I-RODS (±4 centile points) and grip strength (Martin Vigorimeter ±8 kPa) were based on values used in clinical trials.5

The treating clinician made a clinical assessment of Ig dependence (active disease) based on a composite of meaningful deterioration on at least one outcome measure and subjective reporting of functional deterioration by the patient. Once Ig dependence was established, IVIg treatment was restarted. Nadir was marked by date of retreatment. We documented response to retreatment, time to and dose needed to achieve previous baseline.

Those who did not decline were defined as Ig independent (in remission) and were routinely reviewed at 6 to 12 monthly intervals for at least 2 years after treatment discontinuation. The decision and approach to Ig dependency assessment were determined by the treating neurologist, with patient approval and in accordance with national Ig guideline.10

This study was approved by the University College London Hospital Trust clinical governance ethics and consent framework. Individual patient consent was not required for this service evaluation project.

2.1 | Statistical analysis

We present descriptive statistics for group (Ig dependent, Ig independent, cessation, gradual reduction) demographics, baseline clinical, therapeutic and neurophysiological characteristics. We provide mean

![FIGURE 1](image-url) Ig dependence challenge
| TABLE 1 | Clinical characteristics of patients deemed Ig-dependent (active disease) and Ig-independent (remission) |
|----------------|------------------------------------------------------------------------------------------------------------------|
|                | Ig Dependent (Active disease) | Ig Independent (Remission) |
| Number         | 21 | 12 |
| Demographics   |                                             |                             |
| Mean age at onset (range) | 43.4 (22.0-71.0) | 50.6 (25.8-75.1) |
| Sex (M)        | 16 | 10 |
| EFNS/PNS classification |                     |                             |
| Definite       | 19 | 11 |
| Possible       | 2  | 1  |
| Mean delay in diagnosis; y (range) | 4.1 (0.1-12.8) | 3.1 (0.1-19.2) |
| Course of CIDP |                                             |                             |
| Chronically progressive | 13 | 7 |
| Stepwise       | 3  | 0  |
| Atypical CIDP  |                                             |                             |
| MADSAM         | 4  | 3  |
| Focal          | 0  | 3  |
| Supportive criteria investigations—numbers (abnormal) |                     |                             |
| Raised CSF protein | 16 (10) | 10 (6) |
| Abnormal MRI   | 8  (3) | 6  (3) |
| Normal sural SAP with abnormal median SAP | 15 (2) | 11 (2) |
| Nerve biopsy consistent with CIDP | 6 (3) | 3 (0) |
| Mean number of definite electrophysiological criteria fulfilled | 1.4 | 1.9 |
| Individual EFNS/PNS electrodiagnostic criteria fulfilled |                     |                             |
| F-waves prolonged | 1   | 5  |
| F-waves absent  | 4  | 3  |
| Conduction block | 8   | 8  |
| DML >50% of upper limit of normal | 2   | 4  |
| MCV slowing    | 3  | 8  |
| Length of time on IVIg prior to changing/ stopping; mean (range); y | 6.8 (0.4-22) | 4.8 (0.91-15) |

| Clinical outcome measurements | Baseline | Change @ nadir | Restabilization | Baseline | Last FU | Change | Mean (SD) |
|-------------------------------|----------|----------------|-----------------|----------|---------|--------|-----------|
| MRC-SS (Mean (SD))           | 64 (4.0) | −2.3 (3.0)    | 65 (4.5)       | 68.1 (0.9) | −0.8 (1.3) | 67.3 (2.5) |
| Range                         | 57-69    |                | 51-70          | 65-70    |         |        |           |
| I-RODS (Mean (SD))           | 74 (16)  | −15 (16)      | 63 (13)        | 74       | −8.2 (11) | 63 (13) |
| Range                         | 45-100   |                | 40-73          | 57-100   |         | 43-76  |           |
| Mean IVIg dose g/kg/mo (range) | 1.6 (0.7-4) | −54.2%       | 4.0-2)         | 1.0 (0.4-2) | −100%  | 0      |           |
| Time to deterioration/restabilization; Mean (SD), months | 5.0 (4.6) | 2.3 (4.3) |
| Time to withdrawal; M (SD), mo |         |               |                |          | 57 (33.7) |        |           |

Note: Normal CSF protein concentration: ≤0.45 g/L based on local pathology reporting. Abnormal MRI findings: Determined by neuroradiologist as no formal definitions exist for this supportive criterion in 2021 EFNS/PNS CIDP guidelines.8 Nerve biopsy features suggestive of CIDP.8 Complete data set in 14/21 Ig-dependent patients.

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; CSF, cerebrospinal fluid; EFNS, European Federation of Neurological Societies; I-RODS, Inflammatory Rasch-built Overall Disability Scale; MRC-SS, Medical Research Council Sum Score; MRI, magnetic resonance imaging; PNS, Peripheral Nerve Society; DML, distal motor latency; SAP, sensory action potential; MCV, motor conduction velocity.
(SD) change in individual scores (ΔMRC-SS and ΔI-RODS) as the broad range in baseline status within each group resulted in meaningless differences in group scores. Mann-Whitney U tests were used for comparison of continuous variables and Fisher Exact tests for categorical variables. Categorical variables are expressed as percentages and non-parametric variables as median and range. In all tests, 2-tailed P values <.05 were considered significant. Statistical analysis was performed using the statistical package GraphPad Prism version 8.1.2 for Mac, GraphPad Software, La Jolla California, USA, www.graphpad.com.

3 | RESULTS

We identified thirty-three patients on Ig maintenance therapy for CIDP who underwent at least one Ig dependence challenge at NHNN between 2008 and 2018. This was performed by treatment cessation in 16/33 (48.4%) and gradual dose reduction in 17/33 (51.2%). A total of 21/33 (63.6%) were deemed Ig dependent (active disease) and 12/33 were Ig independent (remission), with similar proportions with each approach (Figure 1). Demographic, clinical, therapeutic and diagnostic information on all patients is provided in Table 1.

3.1 | Ig dependent and Ig response (active disease)

Of the 21 Ig-dependent patients, complete documentation of change in clinical scores, time to retreatment (relapse) and time to stabilization was available in 14/21 (Table 1). In 4/14 patients, the Ig dose was reduced gradually, and 10/14 patients attempted immediate Ig cessation. Mean change in MRC-SS at nadir was −2.3 (3.0), and mean change in I-RODS was −15 (16) (Table 1 and Figure 2A). I-RODS change exceed MCID in the majority (6/8 where recorded).

|                                | Baseline | At Time of Deterioration | At Time of Restabilisation |
|--------------------------------|----------|--------------------------|----------------------------|
| MRC Sum Score (Mean; SD)       | 64 (4.0) | 63 (4.3)                 | 65 (4.6)                   |
| Change in MRC Sum Score (Mean; SD) | −2.3 (3.0) |                         |                            |
| I-RODS Logit (Mean; SD)        | 68 (21)  | 53 (12)                  | 85 (11)                    |
| Change in I-RODS Logit Score (Mean; SD) | −15 (16) |                        |                            |
| Months To Deterioration (Mean; SD) | 5.0 (4.6)  |                         |                            |
| Months to Restabilisation (Mean; SD) | 2.3 (4.3)  |                         |                            |
| Number of Patients requiring Greater IVIg Dosing than Prior to Assessing Disease Activity | 2/4 of gradual decrease group | 5/10 of sudden cessation group |

**FIGURE 2** Ig dependence challenge outcomes in Ig-dependent patients (active)
There was no difference in magnitude of deterioration in scores between approaches, but numbers in each group were limited. The mean time from baseline to nadir was 15.08 weeks (SD = 23.7 weeks). The time to nadir was longer with the gradual reduction approach (M: 40.1 weeks, SD = 19.9 weeks) than the cessation approach (M: 17.1 weeks; SD = 15.9 weeks).

There was no relationship between the frequency of maintenance IVIg or dose/kg prior to the Ig dependence challenge and the time to deterioration. The average dose reduction at nadir was 29.75%, and most patients deteriorated at the first dose reduction, 1 deteriorated after 2 dose reductions and another after 4 incremental dose reductions.

Restabilization to previous baseline was achieved in all patients with no difference between mean MRC-SS or I-RODS at baseline and restabilization, independent of approach (Figure 2B). This was achieved sooner with the gradual reduction approach (2.0 weeks, SD: 3.4) than cessation (14.1 weeks, SD: 21.8). A total of 7/14 patients returned to their clinical baseline within a week of restarting IVIg. Three of 10 cessation trial patients and 2/4 patients in the dose reduction group were prescribed a bolus dose (2 g/kg) before restarting their previous regimen. This decision was made because of the magnitude of reduction in MRC-SS and I-RODS at relapse. One of 10 patients received an extended period of double their previous IVIg dose at the same interval and 1/10 received 2 g/kg every 6 weeks for 3 courses before returning to their baseline regimen.

### 3.2 | Ig independent (remission)

Twelve individuals were Ig independent on treatment withdrawal with at least 2 years clinical follow-up. The mean baseline Ig dose: 1.28 g/kg/month, SD: 0.5 g/kg/month and mean treatment duration: 4.39 years, SD: 3.67 years prior to challenge. No individual reported subjective deterioration despite minimal individual changes
in MRC-SS (M: −0.8, SD: 1.3) and I-RODS (M: −8.2, SD: 11) from baseline to last review (Figure 3A). The mean I-RODS change is significantly skewed due to small numbers, and the two patients (men in their 80s) with the most significant change in I-RODS (−14 and −24 points) had developed a parkinsonian syndrome by their last follow-up. Exclusion of these patients from follow-up I-RODS analysis would result in a mean I-RODS change of −1.0 (SD: 3.6) in this group.

Ig independence was determined in 6/12 (50%) by cessation and in the others by gradual dose reduction over a mean (SD) period of 4.75 (2.81) years, range: 0.91 to 5.87 years with 2 to 5 decremental dose reductions of an average 0.4/g/kg at each step (Figure 3B). The total Ig spend from first dose reduction to stopping treatment in 5 individuals was £568 118 (based on Ig cost of £30/g), mean = £113 623 per person.

3.3 | Predictors of Ig dependence/independence

We compared the demographic, clinical, electrophysiological and therapeutic characteristics of Ig-independent and Ig-dependent patient groups, and no statistically significant differences were identified. There was no difference in disease course and no difference in the number of diagnostic criteria fulfilled.

Some potentially relevant subtle differences were noted. The duration of clinical stability on treatment, as defined by within the limits of MCID for I-RODS and vigorimeter and within ±2 points on MRC-SS, was longer for the Ig-independent group: 1.73 years vs 1.26 years in those Ig dependent (active disease), and baseline maintenance Ig dose was slightly higher by 0.62 g/kg/month. Whether minimal clinical fluctuation or a minimal maintenance dose might indicate increased likelihood of Ig independence or not will require assessment in a much larger cohort.

4 | DISCUSSION

This study demonstrates safe and effective methods for differentiating between CIDP patients on maintenance IVIg with active disease vs those in remission. Restabilization to previous baseline was achieved in all Ig-dependent patients. Close clinical monitoring with appropriate outcome measures was sufficient to provide reliable objective evidence for Ig dependence and response in active CIDP. We did not identify any patient, disease, investigational or treatment-related factors that predict disease remission/activity or Ig independence/dependence.

We suggest treatment cessation as a feasible method of promptly, definitively, and safely assessing disease activity. This approach avoids prolonged uncertainty on disease status in the individual and saves on average £100 000 per person Ig spend. Time to restabilization was slightly shorter after demonstrable decline via the gradual dose reduction approach. There were no other differences between the two approaches.

All Ig-dependent patients were restabilized in this cohort, half of which reached their previous baseline within 1 week of retreatment. More than half (8/14) stabilized on restarting their previous IVIg regimen at a mean dose of 1.6 g/kg. This is higher than the maintenance dose used in the restabilization phase of the Polyneuropathy And Treatment with Hizentra (PATH) study.11

In PATH, 35.7% of patients returned to baseline within 13 weeks and another 21% by 17 weeks. In our cohort, where treatment was titrated to clinical response, 100% reached their previous baseline suggesting higher doses, and longer duration of rescue is required in some. Five patients were given a 2 g/kg “bolus” dose before restarting their previous regimen. The two patients with the greatest reduction in I-RODS, 29 points and 43 points on the logit scale, required a more iterative restabilization process. The first patient returned to baseline with 3 courses of 2 g/kg every 6 weeks, and the second patient was treated with double their usual dose for 2 courses, followed by their maintenance dose for 3 months, and at the 3-month review, an extra dose (1.5 g/kg) was prescribed as a one-off at the half-way mark between usual dosing frequency, before returning to maintenance dose.

Definable CIDP relapse as evidence of disease activity is essential to effective study design and interpretation. We know that response rates to steroids and IVIg in CIDP are similar, but whether steroids induce longer remission or not remains unknown.12-16 One RCT comparing pulsed high-dose dexamethasone with prednisolone treatment for 8 months in newly diagnosed patients achieved remission for mean of 11 months in the prednisolone group and 17.5 months in the dexamethasone group.13,15 In another retrospective study comparing oral prednisolone for at least 8 months, pulsed oral dexamethasone or pulsed intravenous methylprednisolone for 6 months in treatment-naïve patients, the median time to relapse was 4 months. The median time to relapse in this Ig-dependent cohort was 3.6 months, comparable to the 4 months recorded by Nobile-Orazio et al (4.0 months). A clear definition of relapse and appreciation of natural history of CIDP is required before this question can be answered through an appropriately designed trial.1,14 The evolution of novel biologic therapies with potential efficacy in CIDP further highlights the timeliness of this issue. Furthermore, there are no formal studies describing an effective approach to restabilization after relapse.

We show that serial monitoring with a combination of subjective reporting of functional status by the individual and objective evidence of deterioration established by multimodal clinical outcome measures was effective in establishing disease activity vs remission in this cohort. Meaningful changes in validated scores were demonstrable with both the cessation and gradual reduction approach. There was a suggestion of better efficiency by cessation, according to time to nadir and Ig cost saving.

However, clinical scores in current use have limitations. Random intra-individual variability- and severity-dependent variation in MCID of common tools is well established.17 There is no consensus on how to interpret and act on changes in scores and decision-making is at the clinician’s discretion. This study highlights the
workload and complexity associated with these decisions. It is unclear how often to attempt cessation trials, and understandably, clinicians may be reluctant to try another cessation trial in patients who were difficult to stabilize after a relapse. We did not formally collect data on patients’ impression of change (PIC) while assessing disease activity, but other groups have shown a strong correlation between changes in disability scores and changes in quality-of-life measures so excessive cessation attempts should be avoided in Ig-dependent individuals.\textsuperscript{18}

Recent work on novel, objective serological biomarkers of disease activity in inflammatory neuropathies is a very promising development in this area.\textsuperscript{19}

Our retrospective study has several limitations as it evaluates a heterogeneous population managed by a group of neuromuscular specialists over a lengthy timespan. We now apply the Lunn et al protocol for IVIg dosing and are vigilant about cessation trials through a dedicated IVIg clinic.\textsuperscript{9} The monitoring of CIDP and MMN has evolved; disease-specific RODS scales and grip strength by vigorimeter were not measured on all included patients from onset. However, we consider this cohort of patients to represent a clinically realistic sample of patients with CIDP and MMN who might attend a specialist neuromuscular centre.

5 | CONCLUSION

Monitoring disease activity remains challenging in CIDP. This study did not identify any obvious predictors of clinical activity/Ig dependence in a cohort of patients on maintenance Ig treatment. However, disease remission can mimic well-controlled active disease and currently treatment withdrawal with close clinical monitoring is the only way of differentiating between these states. Immediate treatment cessation is an effective and safe approach to establishing disease activity, and clinicians should consider this in their treatment algorithms for patients with inflammatory neuropathies.

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CONFLICT OF INTEREST

Dr Lunn was a Primary Investigator in studies for CSL Behring, UCB Pharma, Novartis, Octapharma. He has also received ad hoc consulting fees from CSL Behring, UCB and an honorarium from Terumo BCT. Dr Carr reports Grifols sponsorship for attendance at meeting and honorarium from CSL and Lupin for an advisory role. Dr Kapoor reports Grifols sponsorship for attendance at meeting. The remaining authors have no conflicts of interest.

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