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Office Immunotherapy in Chronic Inflammatory Demyelinating Polyneuropathy and Multifocal Motor Neuropathy

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Abstract

Background—Intravenous immunoglobulin [IVIg], plasma exchange [PE], and corticosteroids are efficacious treatment in chronic inflammatory demyelinating polyneuropathy [CIDP]. IVIg is effective in multifocal motor neuropathy [MMN].

Results and Conclusions—NIS, NIS-weakness, sum scores of raw amplitudes of motor fiber (CMAPs) amplitudes, and Dyck/Rankin score provided reliable measures to detect and scale abnormality and reflect change; they are therefore ideal for office management of response-based immunotherapy (R-IR_x) of CIDP. Using efficacious R-IR_x, a large early and late therapeutic response (one-fourth were in remission or had recovered) was demonstrated in CIDP. In MMN only an early improvement with late non-significant worsening was observed. The difference in immunotherapy response supports a fundamental difference between CIDP (immune attack on Schwann cells and myelin) and MMN (attack on nodes of Ranvier and axons).

Keywords

CIDP; MMN; signs; neurophysiologic tests; immune therapy

INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) has emerged as 1 of an increasing number of treatable neuromuscular disorders usually managed by neurologists.^{1–6} This disease is more prevalent than is generally appreciated; it has an incidence and prevalence similar to that of acute inflammatory demyelinating polyradiculoneuropathy (AIDP or Guillain-Barré syndrome⁷). Unlike AIDP, CIDP only occasionally causes severe generalized paralysis requiring ventilatory assistance but causes prolonged, often severe periods of neuromuscular impairment and disability that require

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treatment.^{8,2} There is strong evidence from prospective controlled clinical trials that corticosteroids,^{9–15} plasma exchange (PE),^{16–18} and intravenous immunoglobulin (IVIg)^{16,19–25} can favorably alter the disease course of CIDP over periods of weeks or months. Late outcomes are also favorably influenced by such treatments (see Discussion). Some reports suggest that a single course of immunotherapy (e.g., corticosteroids) may result in remission of the disease, but typically treatment remissions are temporary. Thus, periodic immunotherapy over prolonged times may be needed.¹² IVIg, and perhaps to a lesser degree corticosteroids, have emerged as preferred treatments,²⁶ although PE is an important adjunctive therapy useful for acute rescue of severe involvement.²⁷ The role of other immunotherapeutic agents such as azathioprine remains unproven.²⁸

By contrast to CIDP, multifocal motor neuropathy (MMN) appears to be less prevalent, and the evidence for its response to immunotherapy (especially to IVIg) is less definite.^{29–33}

In this report we describe and evaluate the endpoints and approaches we have developed for therapeutic trials of CIDP. Later we used the same endpoints and approaches for prospective and periodic assessment of polyneuropathy severity so that immunotherapy could be started, stopped, or adjusted periodically, depending on neuropathy severity and response, i.e., response-based immunotherapy (R-IR_x). Specifically, here we test the performance of the Neuropathy Impairment Score (NIS) and its subscores of weakness (NIS-W), muscle stretch reflexes (NIS-R), and sensation (NIS-S) to score and scale neuropathic severity sensitively and to ascertain the degree of a ceiling effect. Also tested is whether the same scores can be used to reflect worsening or improvement. Next we assess different sum scores of attributes of nerve conduction and their transformations to normal deviates (Z scores) or NIS points. We also test for the correlation of the neurophysiologic tests and different NIS scores and the Dyck/Rankin score. As a further test, these clinical scores are evaluated for their ability to monitor early and late neuropathy outcome in 40 patients with CIDP and 9 patients with MMN. We then considered whether the endpoints and approaches used to evaluate polyneuropathy severity used for research studies and by us for medical practice can be used with benefit by neuromuscular physicians in general. Finally, noting the difference in response to immunotherapy in CIDP and MMN, we consider its implication on our understanding of differences in pathologic mechanisms between CIDP and MMN.

MATERIALS AND METHODS

Study setting, patient selection, and diagnostic criteria for CIDP and MMN

Mayo Clinic, Rochester, MN, USA is a primary and tertiary medical care center where neuromuscular patients are evaluated and treated, including patients with CIDP and MMN. This study is a retrospective review of patients with CIDP (n = 66) and MMN (n = 25) who were evaluated prospectively and treated using semi-masked and standard evaluations before and after R-IR_x. Only patients who had given IRB consent to allow their medical records to be used for research purposes are included in this review. There was sufficient longitudinal data on 40 CIDP and 9 MMN patients, respectively, which allowed assessment of early (from the first period of IR_x) and late outcomes. Most patients were evaluated by 1 author (PJD) using highly standardized approaches for which reference values were available.

The diagnostic criteria for CIDP for purposes of this study were restricted to motor predominant patients with initial progression over periods longer than 2 months, elevated cerebrospinal fluid protein, evidence of nerve conduction dispersion or block with or without slowing, and with disease exclusions. Exclusions included patients with associated known infections (e.g., HIV and hepatitis C) and others with a monoclonal gammopathy of undetermined significance (MGUS). The latter group of patients was excluded, because polyneuropathies associated with IgM MGUS have a different natural history and response to treatment than CIDP, and even neuropathies with IgG, IgA, and IgE MGUS may later develop a lympho- or plasma-proliferative disease (e.g., lymphoma or primary amyloidosis).³⁴ Patients with asymmetric multifocal CIDP (Lewis-Sumner syndrome) were excluded. Patients with metabolic diseases having features similar to CIDP, e.g., hypothyroidism³⁵ and still poorly defined generalized diabetic polyradiculoneuropathies were excluded. The diagnostic features of patients with MMN have been published previously.^{29–33,36}

Standard and semi-masked assessment of polyneuropathy signs, neurophysiologic tests, Dyck/Rankin quality of health score, and other evaluations

The Neuropathy Impairment Score (NIS) was developed to provide a standard and comprehensive assessment of neuropathy signs of weakness (NIS-W), decreased muscle stretch reflexes (NIS-R), and sensation decrease of hands and feet (NIS-S) to evaluate comprehensively mild to severe neuropathic involvement. The NIS scoring copies many of the favorable features of the Mayo Clinic Neurologic Record Sheet in use since the early 20th century.³⁷ In the NIS the scoring of neurologic deficits is based on percentage abnormality between the lower limit of normality, i.e. the fifth percentile considering age, gender, physical characteristics, fitness, and absent function.³⁷ Thus, NIS-W provides scoring of weakness of distributed muscles of head, trunk, and proximal and distal segments of limbs with scoring from 1–4 points in 25% decrements, which provides a range of scores of the 24 muscle groups assessed from 0 points to $24 \times 4 \times 2$ sides = 192 points. NIS-R scores decreased activity of the 5 commonly evaluated reflexes, and scores them in 50% decrements to provide scores of normal (0), decreased (1), or absent (2), with possible scores ranging from 0 to $5 \times 2 \times 2$ = 20 points. In NIS-S, touch-pressure, vibration, joint motion, and pin-prick are evaluated in the toes and fingers and are scored as normal (0), decreased (1), or absent (2) with a range of scores from 0 to $4 \times 2 \times 2 \times 2$ = 32 points. The maximum NIS score therefore is: $192 + 20 + 32 = 244$ points. NIS results were recorded on a standard paper/electronic form for data entry, handling, storage, and analysis.³⁸ As will be discussed, prospective trials have shown that highly proficient judgments of clinical signs can be made by neuromuscular physicians if they use “unequivocal abnormality” as the criterion for judgment of clinical signs.^{39,40}

The standard attributes of nerve conduction that were assessed were: compound muscle action potential (CMAP) amplitudes of motor fibers of ulnar, fibular, and tibial nerves, conduction velocities (MNCV) and distal latencies (MNDL) of motor fibers of the listed nerves, and sensory nerve action potential (SNAP) amplitudes, conduction velocities, and latencies of sensory fibers of ulnar and sural nerves. Studies were typically performed on the left side for standardization purposes. For MMN, CMAPs and SNAPs of the median nerve,

which is commonly involved in this disease, were also assessed. Attributes of nerve conduction (NCs) were expressed as individual and summed raw values, percentiles (as corrected for applicable variables from RDNS-HS reference values^{41,42}), and as normal deviates (Z scores) from percentiles or as points (i.e., percentile values > fifth = 0, > first – fifth = 1, and < first = 2 points). Vibratory detection threshold of the great toe was assessed using the CASE IVc (WR Medical Electronics, Maplewood, MN). As described for attributes of nerve conduction, the threshold values could be expressed as measured units, percentiles, normal deviates, or NIS points. The Dyck/Rankin quality of health score is a modification of the Rankin score.⁴³ In brief, we here describe 3 most commonly observed Dyck/Rankin scores in our treatment cohorts. Score 4 is impairment which interferes with work, activities of daily living, or recreational activities, but the help of a caregiver is not needed. In score 5, the help of a caregiver is needed but for less than 2.5 hours/24 hours. In Score 6, the help of a caregiver is needed for 2.5 to 12 hours/24 hours.

In the early phases of our surveillance of CIDP treatment we also assessed hand-held dynamometry and maximum expiratory and inspiratory respiratory pressure, but these measurements were not continued as outcome measures. We observed that respiratory involvement was a very infrequent manifestation of CIDP and did not occur in MMN, and dynametric assessment of forearm strength did not adequately scale the range of muscle weakness encountered in either CIDP or MMN.

In an attempt to make R-IR_x (described subsequently for use in office-based medical practice) as unbiased as possible, we used semi-masked clinical evaluation of patient neuropathic signs which were graded as abnormal only when they were judged to be unequivocally so.^{39,40} The other measured clinical outcomes (NCs and QSTs) were assessed independently and used reference values obtained from a healthy subject cohort (RDNS-HS).^{41,42}

By semi-masked assessment we mean independent and standard scoring of neuropathy signs, different neurophysiologic tests, and the Dyck/Rankin score without or with as little information as possible about previous or present symptoms or signs, course of disease, or response to treatment. To obtain independent and semi-masked assessments, persons assessed different evaluations without review of previous or concurrent medical records or test results. Neuropathy signs were elicited by grading only “unequivocal abnormality,” i.e., any borderline abnormality was graded as normal (0). As much as possible, tests were judged as normal based on percentile abnormality, i.e., > ninety-fifth or < fifth, taking applicable variables into account. To ensure that all neuropathy signs were actually assessed and scored, a standard NIS form was used, and a scribe (office nurse or neurologic trainee) recorded neuropathy signs item by item as they were elicited. Only after making semi-masked and independent assessments was a medical history taken and previous and other test evaluations reviewed.

Response-based immunotherapy (R-IR_x) using semi-masked assessments

By R-IR_x we refer to the medical practice by which patients are evaluated periodically (frequency determined by disease severity and change with time) using standardized and quantitated measurements with the intent of starting, stopping, or modifying immune

therapy based on assessed severity and change in severity since the last evaluation. The intent was to adjust I_{Rx} to need and therapeutic response. The reasons for adjusting immunotherapy to demonstrated need and response relates to issues of efficacy, safety, and cost. Typically we initiated therapy in static or worsening untreated CIDP in patients who had a Dyck/Rankin score ≥ 4 . I_{Rx} was to be decreased when polyneuropathy impairments were mild and stopped altogether when we judged that it was no longer needed. NIS, summated attributes of nerve conduction, vibratory detection threshold, and Dyck/Rankin score were used to decide whether treatment was efficacious, should be altered, or stopped. Scoring of physical activities, used in later controlled clinical trials, was not used in our longitudinal assessment of patients.^{43,25}

Study objectives and analysis plan

Our study objectives are: 1) describe and evaluate scored neuropathic signs (NIS), specific sum scores of attributes of nerve conduction (NCs), and the Dyck/Rankin score for assessment of early and late outcomes of immunotherapy in CIDP and MMN; 2) describe and evaluate utility of R- I_{Rx} ; 3) determine early and late outcomes from R- I_{Rx} , and 4) consider the reason for response difference between CIDP and MMN.

The endpoints used to assess severity of polyneuropathy were evaluated for how sensitively they identified polyneuropathy, scaled severity, and by the degree of their ceiling effects (beyond which greater impairment could not be scored). They were also assessed for their correlation with objective and quantitative surrogate measures of attributes of nerve conduction and with the Dyck/Rankin health score. Additionally, they were assessed for their ability to monitor a treatment effect when patients were treated with immunotherapy known to be efficacious in CIDP. In this latter assessment, we were especially interested in which test components showed the greatest significant and meaningful improvement. Using the best neuropathic measures, we assessed for early and late outcomes of R- I_{Rx} in CIDP and MMN. We were interested in knowing whether office practice adjustment of I_{Rx} , considering response and need, provided sufficiently adequate semi-masked assessment data to quantitate early and late responses in CIDP and MMN.

RESULTS

Experience with prospective, standard, and semi-masked assessments of neuropathy signs, nerve tests, and health scores in office immunotherapy of immune neuropathies

Patients quickly adapted to our request not to provide the examining physician with information about their symptoms, disease course, or treatment response until neurologic signs, neurophysiologic tests, and disease measurements had all been assessed and entered into permanent medical records. The neurologist (PJD) who performed most of the examinations of signs and judged the Dyck/Rankin score did not recall the specific neurologic examination results or overall scores of previous clinic visits. EMG technologists performed standard nerve conduction assessments independently from the clinical examinations using protocol directives with results reviewed by an electromyographer (WJL). Nerve conduction values were expressed as individual or summed raw measurements, normal deviates, or points from percentiles (see Methods). Needle

electromyography was usually not performed at repeat office visits. After making all semi-masked clinical assessments, we compared change in NIS-W, NIS-R, NIS-S, and raw values of Σ CMAPs of ulnar, fibular, and tibial nerves, VDT value, and Dyck/Rankin scores to previously obtained scores to make judgments about neuropathy severity and change in polyneuropathy severity associated with last treatment and then decided whether a change in kind or dose of immunotherapy was needed.

The use of a standard clinical instrument (NIS), use of a scribe to enter examination results as they were obtained item by item, and avoidance of review of current or previous medical records or of test results could be performed efficiently in a medical office practice setting. Because many of our examinations were standardized, and analyses of results were automated, even in severely affected patients, the NIS evaluation could be performed, recorded, and evaluated in 15–20 minutes. Assuming that values of NCs and VDT results were available at the time of the physician office visit, it was possible to calculate quickly the NIS scores and the other test scores (and combinations of the scores) and compare the values to earlier values.

Adequacy of neuropathic endpoints to detect and scale kind, severity, and distribution of neuropathic signs without a ceiling effect

Adequate characterization and quantification of neuropathic impairment is needed to follow course and treatment effects in CIDP. The adequacy of NIS, NCs, QSTs, and Dyck/Rankin scoring was assessed in the 40 CIDP patients at their first assessment. The distributions of the major endpoints are shown in Figure 1. The distributions provide an indication of the sensitivity, degree of scaling and ceiling effects (beyond which increased abnormality cannot be scaled).

In the CIDP patients, NIS detected and scaled abnormality very well and without a ceiling effect (Figure 1). Values were distributed broadly from 0 to a maximum score of 164 points. No NIS values approached ceiling (i.e., 244 points). The distribution of the scores is also shown as a natural log transformation on the assumption that measurable differences (just noticeable differences) of neuropathy severity might increase exponentially as they do in other neurologic functions, e.g., vision, hearing, and cutaneous sensation. NIS-W also provided a broad range of scores without a ceiling effect. NIS-R provided a broad range of scores, but 10 of 40 were at the maximum value, i.e., at ceiling, therefore limiting their value in scoring of severe cases. NIS-S provided a broad range of values without a ceiling effect, but it performed less well by other criteria (see below).

Different sum scores of attributes of nerve conduction were evaluated for their ability to detect and scale abnormality without a ceiling effect. Summated raw values of CMAPs of ulnar, fibular, and tibial nerves adequately scaled abnormality essentially without a ceiling effect. By comparison when these 3 attributes were expressed as normal deviates or especially as points, pronounced ceiling effects resulted (Figure 1). Sum scores of conduction velocities and distal latencies, which are useful for diagnosis of CIDP, were not as adequate for scaling abnormality; when individual nerve CMAPs are 0, MNCV and MNDL typically cannot be assessed. The Dyck/Rankin score provided a lesser degree of scaling than did NIS or nerve conduction measures (Figure 1).

Correlation between NIS or Dyck/Rankin scores and independently assessed objective quantitative nerve conduction measurements

Because attributes of nerve conduction are objective and quantitative (albeit surrogate) measures of severity of polyneuropathy, it is important to assess their correlation with direct measures of weakness, reflex abnormality, and sensation loss, i.e., NIS and the Dyck/Rankin health score, the latter depending more on individual physician performance and judgment (Supplementary table S1, available online). Statistically significant correlations of 11 of 12 neurophysiologic tests with NIS were observed, a strong confirmation that NIS and neurophysiologic tests measure the same phenomenon, i.e., polyneuropathy severity. Also, it is of note that vibratory detection threshold using CASE IVc also showed significant correlation with NIS and NIS-S but not with NIS-W. Somewhat lower numbers of neurophysiologic measures correlated with NIS-W and NIS-S. Eight of 12 neurophysiologic measures correlated significantly with the Dyck/Rankin score (Table S1). Among the composite measures of attributes of nerve conduction, CMAPs performed better than did MNCVs or MNDLs. Ulnar and sural SNAPs performed better than composite measures of MNCVs or MNDLs.

Performance of neuropathy signs, neurophysiologic tests, and Dyck/Rankin health outcomes in early outcomes of R-I_{Rx} in CIDP

The third approach used to assess performance of polyneuropathy endpoints was their ability to monitor severity of polyneuropathy for significant improvement of the endpoints from use of therapy known to be efficacious (from previously conducted controlled clinical trials) from the first period of treatment of the CIDP cohort. The results of this evaluation are shown in Supplementary table S2 (available online). Improvement of all 21 measurements was observed with 14 of the endpoints and was significant statistically. Among NIS scores, NIS, NIS-W, and NIS-R showed large and significant improvements. VDT as measured with CASE IVc also showed significant improvement. Summated ulnar, fibular, and tibial CMAPs (using raw values) showed significant improvements. Other composite NC scores of CMAPs and SNAPs also showed significant improvement, but other summated NC scores did not (i.e., MNCVs, MNDLs, F-waves, SNAPs, SNCVs).

Early and late outcomes from R-I_{Rx} in CIDP

In Figure 2, we plot the change of NIS, raw measures of Σ CMAPs of ulnar, fibular, and tibial nerves (mV), and Dyck/Rankin scores over prolonged periods of immunotherapy (R-I_{Rx}) in patients with CIDP. In the inserts, drawn to scale, we show lines representing beginning and end median values for early (first treatment period) and late outcomes. Considering NIS, there was dramatic early improvement followed by a small later further improvement. All 40 CIDP patient responses are reflected in the early responses. Of the 40 CIDP patients, 37 had late outcomes, 27 were receiving immunotherapy at last follow-up, and 10 were in remission or had recovered. Of those without late responses, 1 patient was removed from treatment because of concurrent and fatal cardiovascular disease, and 2 could not be evaluated for other reasons. The above data provide confirmation that immunotherapy (notably IVIg, PE, and corticosteroids) is associated with marked early and late improvement of CIDP. It provides additional evidence that R-I_{Rx} can be used to monitor and

adjust I_{Rx} periodically to response and need. In some cases, more frequent and larger dosages of I_{Rx} or multi-modality I_{Rx} were needed and used (e.g., PE followed by IVIg) to achieve a favorable response. More typically, it was possible to reduce I_{Rx} from the dosage and frequency used at first treatment, thus decreasing treatment morbidity and cost. In some teenaged patients, IVIg could be reduced to 0.05 gm/kg given at every 6 week intervals; however when it was decreased even further or stopped altogether, disease exacerbations occurred. With experience we came to use a standard treatment regimen initially, e.g., IVIg in doses of 0.4 gm/kg twice weekly (typically Monday and Thursday or Tuesday and Friday) for 4 weeks and then weekly for another 4 weeks, at which time patients were re-evaluated by NIS, NCs, VDT, and the Dyck/Rankin score. We then adjusted treatment, increasing or decreasing treatment (kind, dose, or frequency) depending on measured neuropathic severity, change in severity, and response to treatment. A lack of a favorable response to I_{Rx} (e.g., IVIg) was used to raise the question of the correctness of the diagnosis of CIDP and adequacy of treatment. Typically, as has been demonstrated above, there was a favorable response to IVIg or PE, but occasionally when neither treatment was efficacious, corticosteroids (given orally or intravenously) were used, sometimes resulting in an unequivocal beneficial response.

Early and late outcomes of I_{Rx} in MMN

The data are shown in Supplementary table S3 and Figure 2. Note that the early and late responses are strikingly different from CIDP. Use of IVIg (0.4 gm/kg) typically given twice weekly for 3 or 4 weeks and then weekly for another 4 weeks resulted in a significant early fall in NIS-W, but no significant improvement of other endpoints (Table S3). Over prolonged treatment periods, median endpoint scores did not improve but worsened, albeit not to statistically significant degrees. None of our MMN patients recovered.

DISCUSSION

In this study, we report that Neuropathy Impairment Score (NIS) sensitively and comprehensively scales neuropathic severity without a ceiling effect and correlates significantly with independently assessed neurophysiologic measures. Among NIS subscores, weakness (NIS-W) performed best. This score recognizes very mild involvement, scales different degrees of severity, and does so without a ceiling effect even in very severe cases. The muscle stretch reflex score (NIS-R) performs less well than NIS or NIS-W and has a large ceiling effect.

Composite surrogate measures of attributes of nerve conduction also performed well in detecting and scaling polyneuropathy severity. Although they are surrogate measures, because they are objective and quantitative indications of severity, they were used by us as confirmatory indications of therapeutic response. Sum scores of the raw measures of CMAPs of ulnar, fibular, and tibial nerves performed better than their transformation to normal deviates (Z scores) or NIS points; the latter resulted in higher ceiling effects. The summated raw values of CMAPs of motor fibers of limb nerves correlated strongly with NIS and Dyck/Rankin scores. By comparison, motor nerve conduction velocities and distal

latencies of these nerves, which are especially useful for diagnosis,¹⁷ did not perform as well for monitoring immunotherapy response.

Can the good outcomes of clinical signs and neurophysiologic measures demonstrated here be generalized to clinical performance at other medical centers? We assume it can, but only if assessments are done with the needed proficiency (accurately and with high intra- and inter-rater agreement). The approaches which should be used to achieve this degree of proficiency of neuropathy signs, attributes of nerve conduction, and quantitative sensation testing have been tested and described in our previous Clinical Neurophysiologic Trials.^{39,40,44–46} Thus, CIDP and MMN patients are typically evaluated by highly trained neuromuscular physicians. These physicians should be able to reliably and reproducibly score neuropathic signs if they record and quantitate only “unequivocal abnormality” – a finding of CI vs. NPhys Trials 1 and 2.^{39,40} Using trained clinical neurophysiologists, attributes of nerve conduction are increasingly done accurately and proficiently at many medical centers.^{44,45} Composite raw scores of ulnar, fibular, and tibial nerve CMAPs and SNAPs are readily measured in high quality EMG laboratories. The CI NPhys Trial 5⁴⁶ has shown that standard and referenced quantitative sensation test scores can be done accurately and without intra- and inter-rater difference at different medical centers.⁴⁶ The Dyck/Rankin score is easily understood and used. In short, the major outcomes found here to be useful for monitoring treatment response in CIDP are ones that can be done proficiently at multiple medical centers.

Are there special concerns and limitations of the composite scoring of neuropathic signs and neurophysiological tests? The first limitation is inadequacy of somatotopic evaluation of sensation loss. While sensation loss typically is length-dependent in CIDP and does not occur in MMN because proximal limbs and trunk are not evaluated in NIS, it could be a problem in some patients who have more generalized sensation loss. Smart Somatotopic QST can be used to remedy this short-coming.^{47,46,48} The second concern is whether the different measured endpoints assessed here are adequately weighted. Whereas NIS comprehensively assesses observed weakness and muscle stretch reflex abnormality, it remains somewhat unclear what weights should be given to observed sensation and neurophysiologic test abnormalities, a subject discussed in a recent paper.⁴⁸

The second aim of this study was to describe and assess semi-masked independent clinical and neurophysiologic tests and response-based immunotherapy. The endpoints and general approaches utilized were modifications of approaches and endpoints first used in controlled clinical trials of immunotherapy in CIDP and MGUS neuropathies.^{16,21,49} The controlled clinical trial approaches were modified here for use in clinical practice to include: 1) introduction of independent semi-masked neuropathic assessments and 2) response-based immunotherapy of known efficacious therapies. For these purposes, we retained the polyneuropathy endpoints found useful in therapeutic trials. We have found that independent and semi-masked assessment of neuropathy signs using NIS, neurophysiologic tests, and the Dyck/Rankin score can be performed quickly and efficiently in office medical practice. With explanation, patients understand that improved data are likely to come from such standard, independent, and semi-masked assessments. The approach is more quantitative and likely to be more unbiased than when patients are assessed and treated by usual clinical methods.

We judge that the independent and semi-masked assessment and R-I_{Rx} approach described here can be used readily at many, perhaps most medical centers. Most modern medical centers have the neuromuscular experts to make the clinical judgments. To make such judgments it is important for clinicians to determine abnormality specifically taking age, gender, physical attributes, and fitness into account.^{41,42} Abnormality of neuropathic signs should be graded only when unequivocal abnormality has been found. Of the attributes of nerve conduction for purposes of assessing therapeutic efficacy, sum scores of the raw values of the CMAPs of ulnar, fibular, and tibial nerves have been found to provide meaningful quantitative measures of polyneuropathy severity. The Dyck/Rankin score was found to be useful in judging when to start, stop, or alter immunotherapy and can be used readily at most tertiary medical centers. An important insight to come from our medical practice review of immunotherapy in CIDP is that it should be adjusted to need and response. Periodic evaluation at regular intervals of time, using the endpoints available at all medical centers make this possible.

This study also provides information about the early and late outcomes from R-I_{Rx} in CIDP and MMN. In our CIDP cohort, immunotherapy (IVIg, PE, and corticosteroids) was associated with unequivocal early and late favorable responses. Thus of 21 overlapping endpoints assessed after first treatment of CIDP, all showed early improvement with I_{Rx}, and 14 of them were statistically significant. The magnitude of the improvement was often large. To illustrate, the median NIS point values from the first period of I_{Rx} fell from a median value of 68 to 38 NIS points and the NIS-W fell from 55 to 22 points; this is a large and unequivocal improvement. Typically, improvement occurred over a short period of 2–3 months. As noted in the introduction, comparable degrees of initial improvement have been observed in controlled clinical trials assessing PE and IVIg. By adjusting I_{Rx} to need and response, it was possible to maintain or even improve CIDP patients' neuropathic status over the ensuing years. This further improvement was recognized by comparison of neuropathic endpoints and by clinical improvement to the point that further treatment was not needed in more than one-fourth of patients. We emphasize that the late improvement developed despite some of them receiving increasingly smaller and less frequent dosages of immunotherapy. By the end of our late surveillance period, 10 of 40 patients no longer received I_{Rx}, a similar remission and recovery rate to that reported previously.^{1,20,50–52,14,4}

The response to immunotherapy in MMN was strikingly different from CIDP, with significant improvement being demonstrated only for NIS-W and only for the initial period of treatment. Contrary to what was observed in CIDP, sum scores of CMAPs of motor fibers of limb nerves did not improve. Considering long-term neuropathic status, NIS-W tended to worsen, although not to a statistically significant degree. However, it should be noted that when intermittent IVIg treatment was withheld, patients reported worsening of some key motor functions. Considering patient reports, significant improvement of NIS-W with first treatment, lack of verification of this improvement by assessment of composite scores of raw values of CMAPs, it appears that IVIg may have a useful role in prevention of worsening rather than being associated with measurable improvement.

This difference in response to immunotherapy in CIDP as compared to MMN needs to be considered. One possibility is that the poor response in MMN relates to lack of power in our

and other studies, i.e., too few patients. However, in CIDP, unequivocal improvement could be recognized from use of PE or IVIg in similar small groups of patients.^{16–18} Despite using similar doses of immunotherapy, late outcomes were strikingly different between the 2 diseases. In CIDP with intermittent R-IR_x there was a large measured improvement and, in addition, many patients had recovered or were in remission. By comparison in MMN, patients did not show this degree of improvement despite similar long periods of treatment.

The difference in treatment response between CIDP and MMN demonstrated previously and here is probably explained by neuropathologic and mechanistic differences between the 2 disorders. Although still incompletely understood, the disease attack in CIDP appears to be on Schwann cells and myelin, which results in inflammatory demyelination (and remyelination) of peripheral nerve fibers and with some concomitant, perhaps secondary, axonal degeneration.² In MMN the immune attack appears to be on nodes of Ranvier with little evidence for overt inflammation, no de- or remyelination,^{53–63} and evidence of significant axonal injury leading to axonal sprouting, particularly with longer disease duration.⁶⁴ In early stages of the disease, targeted fascicular biopsies may appear normal and support the hypothesis of a functional block at the nodes of Ranvier. In CIDP, segmental demyelination associated with neurophysiologic abnormalities of conduction block, dispersion, and low conduction velocity appears to be an early event, and axonal degeneration occurs as a later and milder event. In MMN, conduction block and axonal degeneration appear to be primary and major events. The pathologic abnormalities in CIDP are more generalized as compared to MMN. The predilection for conduction block and site of axonal injury (as inferred from biopsied median nerves at this site⁶⁴) in the mid forearm region of the median nerve and other focal sites of involvement remains unexplained.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

AIDP	acute inflammatory demyelinating polyradiculoneuropathy
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
CMAP	compound muscle action potential (amplitudes)
IR_x	immunotherapy

IVIg	intravenous immunoglobulin
Semi-masked	the approach we used to assess neuropathic signs, symptoms and disability with the observer “masked” as to previous and current other examination and test results
MGUS	monoclonal gammopathy of undetermined significance (IgA, IgE, IgG, IgM)
MMN	multifocal motor neuropathy with persistent conduction block
NIS	Neuropathy Impairment Score (points)
NIS-R	the reflex subscore of NIS
NIS-S	the sensation subscore of NIS
NIS-W	the weakness subscore of NIS
PE	plasma exchange
R-I_{Rx}	response-based immunotherapy

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Figure 1.

The distribution of outcome measures assessed at baseline in the cohort of 40 CIDP patients. The observed distribution provides an indication of sensitivity, scaling, and ceiling effects. NIS and NIS-W provide sensitive scores and scaled abnormality without a ceiling effect. NIS reflexes (NIS-R) has a 25% ceiling effect. Among different sum scores of compound muscle action potential (CMAP) amplitudes, raw values performed best with the lowest ceiling effects. Transformation of CMAPs to normal deviates or points resulted in higher than desirable ceiling effects. The Dyck/Rankin score performed well, although it provided a limited scaling of neuropathic abnormality.

Figure 2.

Individual CIDP patient values of NIS (points), Σ CMAPs (mVs), and Dyck/Rankin scores assessed serially over the duration of the study. Response-based immunotherapy (R-IR_x) of IVIg, plasma exchange, or corticosteroids was used by methods and criteria described in the text. The first point of each patient's line represents the baseline value. The second point is the value after the first treatment (the early treatment). Subsequent points on the line represent assessed values related to R-IR. In the inserts, drawn to scale, we show the median onset and endline values of early and late outcome from R-IR_x. Observe that in CIDP there

is an unequivocal early improvement in the 3 outcome measures (decrease in NIS, increase in sum scores of CMAPs, and decrease of the Dyck/Rankin score) and a further late improvement. As described in the text, 10 of 40 CIDP patients at last evaluation were either in remission or had recovered.

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