~~Monitoring~~ Assessment of outcome measures to monitor ~~during individualization of m~~maia~~i~~ntenance IVIg therapy ~~immunoglobulin treatment~~ in patients with chronic inflammatory neuropathy

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Abstract

Introduction: To evaluate the utility of different outcome measures ~~in the~~ to monitor dose adjustment of intravenous immunoglobulin (IVIg) therapy ~~assessment of the individual~~ in patients with chronic inflammatory neuropathy (CIN). ~~during intravenous immunoglobulin (IVIg) dose adjustment.~~

Methods: We assessed the ~~individualized~~ adjustment of IVIg maintenance therapy ~~reatment~~ in 20 patients by~~while~~ regularly monitoring grip strength (GS) using a Martin vigorimeter, Rash- Overall Disability Scale R-ODS, and quality of life using the SF-36 questioner. These measures were regularly performed at home by the patient. We also assessed the ~~and~~ extended MRC sumscore at each hospital visit of the patien for therapoy. ~~Thirty healthy controls w~~We also ~~r e~~ enrolled 30 normal subjects to measure ~~any~~ the possible training effect of daily GS measurement at home and the ~~of improvement with time and to analyze~~ random fluctuation of GS.

Results: 'Random' fluctuations of GS for one day occurred in 33-73% of patients, but for at least four consecutive days only in 10-23% of patients. Clinically-relevant change was detected by MRC in 14 (93%) patients, by RODS in 11 (73%) patients, and by GS in 8 (53%) patients. Early sensitivity was greatest for RODS (73%), followed by GS (53%), and MRC (27%).

Discussion: Home monitoring of outcome measures objectively assisted clinical decision during individualization of IVIg treatment.

Key words: chronic inflammatory demyelinating polyneuropathy; CIDP; multifocal motor neuropathy; outcome measures; grip strength; intravenous immunoglobulin

Introduction

Current guidelines for chronic inflammatory neuropathies (CINs) recommend individualizing maintenance intravenous immunoglobulin (IVIg) treatment using the minimum effective dose and periodically attempting dose reduction or interval lengthening trials to establish the need for ongoing therapy (1-5). Since there are no valid laboratory biomarkers for CINs, there is the recommendation to use objective outcome measures ~~are recommended to~~ to optimize treatment (1-7). There is still no consensus on how many and which outcome measures ~~should~~ should be used in routine clinical practice (8). Moreover, ~~we still do not know~~ it is still unlcear which minimum clinical important difference (MCID) cutoff values are appropriate for individual patient assessment (8). Although different MCID thresholds have been proposed for various outcome measures, with positive results in randomized clinical trials, it is not clear whether they are appropriate in clinical practice. For instance, in the ICE study, almost 26% of the patients treated with placebo showed improvement in their grip strength (GS) greater than the proposed MCID cutoff value of 8 kilo Pascal (kPa) (9,10). ~~This figure was confirmed by a~~A recent study ~~showing~~ showed however that random fluctuations ≥ 8 kPa occurred in 27% of patients (11). It is also uncertain whether frequent measurements with outcome measures may provide useful information to guide clinical decision on adjustment of treatment. A recent study showed that the daily self-monitoring of GS demonstrated improvement after IVIg in some patients with CINs that may be indicative of treatment dependency, although this was not prospectively confirmed (11). In this study, we aimed:

1. To investigate the clinical utility of different outcome measures, and their MCID cutoffs, in the assessment of the individual patient with CIN during IVIg dose adjustment.

2. To evaluate the role of the home monitoring of different outcome measures in informing clinical decision on adjustment of IVIg treatment in the individual patient with CIN

Methods

Inclusion criteria

Chronic inflammatory neuropathies patients

We proposed the study to ~~all our~~ patients with a diagnosis of any type of CIN, under maintenance IVIg therapy who had performed ~~treated with regular long term IVIg (a~~at least three ~~previous~~~~past~~ treatment ~~courses~~~~cycles)~~ at Humanitas Clinical and Research Hospital, Milan, Italy. No patient was excluded for a possible physical or mental ~~Patients unable to reliably perform GS assessment (e.g. significant cognitive or visual~~ impairment~~)~~ that might have limited the capacity to perform home assessments ~~or with other medical conditions affecting their grip (e.g. painful hand arthritis) would have been excluded though none met these criteria. .~~

Healthy controls

We recruited 30~~Thirty~~ healthy controls from hospital personnel, relatives, and friends ~~were also recruited~~ to analyze random fluctuations in GS and to measure any possible training effect of GS improvement with time. Eligibility criteria were~~:~~ normal cognitive function, preserved vision, absence of any impairment affecting upper limb function.

Study design

We trained p~~Subjects (p~~atients and healthy controls~~)~~ ~~were trained~~ to ~~perform~~ measure at

home GS using a Martin Vigorimeter and to report ~~cord~~ the measurements on a standard form~~,~~ ~~which~~ that patients ~~patients~~ returned at ~~their~~ each hospital ~~next~~ visit and healthy controls at the end of the study. Subjects were asked to perform~~measure once every day,~~ at the same time every~~each~~ day, three consecutive maximum voluntary contractions (healthy controls using both hands and patients using the most affected hand), and to record to the nearest ~~1~~ one kilo Pascal (~~.~~ kPa). We asked to the ~~P~~patients ~~were asked~~ to measure ~~their~~ GS at home for the entire study period and we instructed~~. H~~ healthy controls ~~were instructed~~ to measure GS at home for one month.

During the study period, we maintained ~~in each~~stabilized patients ~~patient, dosage of~~under IVIg therapy with the same~~IVIg was maintained stable~~ dose for one course during which we performed all the measurement. Based on the results of this baseline assessment, we progressively adjusted the dose of IVIg~~n individualized according to the results of the assessment at baseline: 1) i~~. In objectively stable patients, ~~the~~ IVIg dose was progressively reduced (usually every second IVIg ~~dose~~course) until ~~appearance of~~ clinical worsening, ~~then~~ after which the dose was restored ~~to~~ at the lowest effective level. In~~; 2) in objectively unstable~~ patients with an unsatisfactory response, we ~~the IVIg dose was~~ progressively increased IVIg dose was to~~until the reach~~ obtain~~of the~~ maximal~~um~~ improvement. We defined ~~C~~clinical stability ~~was considered when~~if ~~both~~ the patients had maintained ~~two following criteria were met: 1)~~ an unchanged neurological examination ~~over the past three treatment dates, (2)~~with no more than one point change in the ‘extended’ MRC sumscore’ (eMRC sumscore~~SS~~) (0-120) ~~changed by ≤ 1 point~~ over the previous three courses~~treatment dates~~.

We used ~~T~~the following outcome measures ~~were chosen~~ to monitor the patients during the study: (1) GS (assessed on a daily basis), (2) Rasch-Overall Disability Scale (R-ODS) (assessed on a weekly basis), (3) SF-36 scale (assessed on a daily basis). The patient measured these parameters at home~~, all performed by the patients themselves at home~~. (4) We measured the ~~, and (4)~~ eMRC~~SS~~ sumscore ~~assessed~~ in the hospital at the time ~~outpatients visits to hospital at the time o~~of IVIg

infusions. ~~In order to minimize the influence of GS measurement on patients' subjective impression on health, we~~We asked to the patients to complete the SF-36 scale before measuring GS to minimize the influence of GS measurement on their impression on health ~~every day~~. We defined a clinically ~~important~~ relevant change an improvement s ~~of at least~~≥ 4 centile points on the I-RODS score for patients with typical or atypical chronic inflammatory demyelinating polyradiculoneuropathy ~~or (~~CIDP) ~~(typical or atypical)~~ (12), ~~≥ 4~~at least 4 raw points on the MMN-RODS for patients with multifocal motor neuropathy ~~(or~~ MMN) (~~as~~ the centile transformation is not published), at least ~~≥~~ 2 points on the eMRC sumscore~~SS~~ (10). We based the~~, while~~ MCID threshold for GS on the results of daily ~~was not defined a priori but chosen based on the results of the GS~~ fluctuation ~~analysis~~ observed ion healthy controls (see below). Due to the variable~~It is uncertain what change in MRC indicates~~ definition of MCID ~~a clinically important improvement~~ on the MRC (10)~~in an individual patient~~, we ~~and three MCID thresholds have been proposed (2 points, 3.53 points, and 3.6 points) (10). To determine which threshold is more sensitive to identify treatment response in an individual, we repeated~~performed the ~~the~~ analysis ~~for MRC us~~using either~~first~~ ≥ 3 ~~points and then~~and ≥ 4 points for each patient~~as the MCID threshold.~~. We assessed the ~~C~~concordance between patients' subjective impression on health and clinical change ~~was determined~~ by calculating for each outcome measure the number of days with clinically significant change ~~on which~~ subjective feeling of ~~patients~~ improvement~~had self-reported improvement~~. During the study period, patients were longitudinally examined by the same clinician (P~~.~~E~~.~~D~~.~~).

We defined ~~B~~baseline ~~for~~ GS~~, was defined as~~ the *mean* (or *maximum*) of six ~~GS~~ measurements performed by the patient~~s~~ at home~~,~~ the first day of ~~the first~~ IVIg treatment ~~infusion of the study~~, and by ~~healthy~~ controls on the first day of the monitoring. ~~We chose to measure baseline GS at home, instead of at the outpatient visit to hospital, to avoid possible fluctuations of GS caused by the use of a different seat (e.g. different type of chair) at home.~~ We asked patients to use the same seat for the entire duration of the monitoring. We defined ~~T~~the more affected hand in the patients ~~was defined as~~ the hand with lower GS at baseline (or ~~if equal, then~~ the dominant hand if

equal). Written informed consent was obtained from all participants. The study was approved by our institution's ethic committee.

Assessment tools/scales

Impairment

Grip strength measurement was performed using the Martin Vigorimeter in a standardized way (13). Muscle strength was assessed bilaterally using an 'extended' version of the Medical Research Council (MRC) sumscore performed on 24 muscles (range 0-120), including upper arm abductors, elbow flexors, elbow extensors, wrist extensors, finger extensors, thumb opponents, first dorsal interosseous, abductor digiti minimi, hip flexors, knee extensors, foot dorsal and plantar flexors muscles. We decided to ~~chose to use an '~~extend~~ed~~ the~~'~~ usual version of the MRC sumscore (0-60) to capture changes in a larger number of proximal and distal muscles that may be selectively o r predominantly affected in some patients. ~~for two reasons: (1) it is the most commonly used version in routine clinical practice and (2) it is likely to be more sensitive than the classic version used in clinical trials (0-60).~~

Disability

We used t~~T~~he I-RODS for CIDP patients and the MMN-RODS for MMN patients that were reported to be~~chosen as~~ disease-specific ~~outcome~~ measures of~~to assess~~ disability (14,15).

Patients' self-reported impression of change in general health

We use a modified Short-Form 36 questionnaire (Medical Outcomes Trust, Boston, MA, USA; SF-36) t~~T~~o assess subjective global change in health. We modified question 2 of this questionnaire into: ~~we used a modification of question 2 of the Short-Form 36 questionnaire (Medical Outcomes Trust, Boston, MA, USA; SF-36). Patients were asked~~ 'Compared to the day before the first infusion of IVIg of the study, at baseline, how would you rate your health in general

now?' The possible response ~~and to choose one~~ were~~of the following responses:~~ 'much better', 'somewhat better', 'about the same', 'somewhat worse' or 'much worse'. These answers ~~is was~~were then ~~-~~dichotomized as either 'improved' ('much better' or 'somewhat better') or 'not improved' ('about the same' or worse). To facilitate the answer, in the standard form, each of the five response options has been associated with a smiley face with different expression.

Analysis of ~~R~~random fluctuations and training effects of GS in healthy controls~~analysis~~

We ~~analysed~~analyzed random fluctuation (day-to-day variation) of GS in healthy controls ~~for two reasons: (1)~~to determine ~~to assess~~ whether it is more reliable the~~to base~~ analyses o~~n~~ the *maximum* or the *mean* of the three GS measurements in~~on~~ one day and ~~; (2)~~ to assess the specificity of the used ~~two published~~ MCID thresholds for GS. We assessed ~~(~~8 kPa and 14 kPa~~)~~ (10), and ~~of other~~ two intermediate ~~cutoff~~ values (10 kPa and 12 kPa). ~~chosen arbitrarily as intermediate between the previous two.~~ For each subject, ~~on each day,~~ we calculated ~~both~~ the '*maximum* daily GS' and the '*mean* daily GS' from ~~the~~ three measurements in the ~~analysed~~analyzed hand~~, and separately performed all the following analyses for each~~. We defined~~For the~~ the baseline '*maximum* daily GS' ~~analysis', baseline was defined as~~ the maximum of ~~the~~ six GS measurements ~~obtained~~ at baseline. ~~For each control subject, we~~ We also calculated for each patient, the maximum absolute deviation (negative or positive) on any day from baseline. ~~Across~~ For the whole group, we calculated the median and maximum value of these deviations. For each subject, we calculated the proportion of days in which the daily value deviated by at least 8, 10, 12 or 14 kPa from baseline ~~(e.g. 3 out of 21 days = 14.2%)~~, and, for ~~across th~~the whole group, ~~we calculated~~ the median of this proportion. We use

~~*Training effect on healthy controls*~~

~~A~~a paired t-test ~~for~~ paired ~~data was used~~ to evaluate ~~any~~ the training effect on control subjects, comparing the *mean* GS of the first three days with the *mean* GS of the last three days one

month later~~(after approximately 1 month)~~. ~~In order to avoid a ceiling effect in healthy controls with GS baseline values near to 160 kPa (the highest value measurable by the Martin Vigorimeter), the non-dominant hand was chosen for the analysis.~~ Mean difference and 95% Confidence Interval (95% CI) were calculated.

Results

Baseline characteristics

Patients

Twenty ~~unselected~~ patients (10 CIDP and 10 MMN) were included. Demographic and clinical features at baseline are summarized in Table 1. Median treatment length was 5 years. Median IVIg dose was 0.22g/kg/week. All patients fulfilled the EFNS/PNS diagnostic criteria for probable CIDP or MMN, except patient 3 (P3) and P17 (possible CIDP) and P16 (possible MMN) (2,3). All included patients had reduced GS in at least one hand compared with normal reference values (16). The mean number of days in which patients reported the measurements was 172 (range 67-667). No patient reported any significant medical event (unrelated to the neuropathy) that might have affected GS during the monitoring.

Healthy controls

Thirty healthy controls (16 males, 14 females; mean age 49 years, range 21-72 years) participated. The majority of patients~~Most~~ (73%) w~~a~~ere~~s~~ right-handed. The dominant-hand median GS at baseline was 82 kPa (range 50-158). The non-dominant-hand median GS was 76 kPa (range 45-152). Fourteen (47%) healthy controls had reduced GS in at least one hand compared with normal reference values (10 females and 4 males with a mean age 48 years, range 29-70 years; reduced GS in both hands in 8, only in the non-dominant hand in 6; mean deviation from normal reference value: 15 kPa [range 3-26 kPa] in the dominant hand and 13 kPa [range 3-29 kPa] in the

non-dominant hand) (16). No healthy control reported any significant medical event that might have affected GS during the monitoring.

Random fluctuations and training effect analysis in healthy controls

Table 2 summarizes the results of the random fluctuation analysis in healthy controls. The *mean* daily GS deviated ~~at least~~ 8 kPa or more (above or below) from baseline in 22 (73%), ~~at least~~ 10 kPa or more in 18 (60%), ~~at least~~ 12 kPa or more in 14 (47%), and ~~at least~~ 14 kPa or more in 10 (33%) healthy controls. The *maximum* daily GS fluctuated more than the *mean* daily GS. The maximum deviation of the *mean* daily GS from baseline was 24 kPa while the maximum deviation of the *maximum* daily GS was 22 kPa (full results for individual patients shown in supplementary table 1). ~~Since there were~~Given the large fluctuations of ~~the~~ daily GS in healthy controls~~, with the four criteria showing insufficient specificity, ,~~ we calculated the number of patients in whom the *mean* GS deviated ~~by ≥ the MCID thresholds~~ for at least four consecutive days. This occurred in 7 subjects (23%) ~~*Mean* daily GS deviated for at least four consecutive days by~~*for* 8 kPa ~~in 7 (23%)~~, ~~by 10 kPa in~~ 6 subjects (20%)~~, for 10 kPa, 4 subject for by 1~~12 kPa ~~in 4~~ (13%), and 3 subject ~~by 14 kPa in 3~~ (10%) for 14 kPa~~healthy controls~~. The same figure for the *Maximum* daily GS ~~deviated for at least four consecutive days by~~were 11 subjects (37%) for 8 kPa in ~~11 (37%)~~, 7 (23) for~~by~~ 10 kPa in 7 (23%), 5 (17%) for~~by~~ 12 kPa ~~in 5 (17%~~), and 3 (10%) for~~by~~ 14 kPa ~~in 3 (10%) healthy controls~~ (full results for individual patients shown in supplementary table 2). ~~Since daily random fluctuation was less in *mean* than *maximum* daily GS value,~~ We therefore ~~we u~~used the *mean* daily GS for four consecutive days~~value~~ for ~~all the~~ subsequent analyses.

~~**Lack of training effect in healthy controls**~~

No significant difference was observed between GS at baseline and after a mean of 29 days (range 24-34) of monitoring in healthy controls. Mean (SD) GS in the non-dominant hand was 82

kPa (29.6) at baseline and 85.3 kPa (30.3) [p=0.4232] at 29th day; mean (SD) difference was 3.59 kPa (4.7) (95% CI -12.4; 5.2). Mean (SD) GS in the dominant hand was 88 kPa (31.2) at baseline and 89.9 kPa (30.7) [p=0.7530] at 29th day; mean (SD) difference was 1.46 kPa (4.6) (95% CI -10.5; 7.6).

Intravenous immunoglobulin treatment adjustment

APatients P1-P11, P13-15, and P17-20ll but two patients (12 and 16) were clinically stable at study inclusion. In all these patients, the IVIg dose was progressively reduced by a mean 43% (range 10-100%) until clinical worsening or IVIg suspension. We reduced the IVIg dose maintaining the treatment interval stable in all but patient Only in P13 in whom we lengthened the treatment interval between IVIg infusions upon patient's request(personal choice of the patient), while. We observed an in the other patients we reduced the IVIg dose maintaining the treatment interval stable. Oobjective clinical worsening was observed inin 13/18 (7265%) patients (P1-P9, P14, P15, P17, P18). In two of these patients (P2, P14), IVIg maintenance dose was reducedthe dose was increased to a level inferior to the baseline level , while in the other patients the previouswe restored the baseline dose dose was re-established. Five (285%) patients (P10, P11, P13, P19, P20) suspended IVIg treatment without clinical deterioration. .

Patient P12 and P16 were unstable at study inclusion. P12 had had a rapid worsening which was likely caused by aafter surgical intervention of radical prostatectomy occurred performedtw two weeks before study inclusion. After monitoring with the outcome for one monthmeasures for one cycle, we his dose of IVIg was increased IVIg from 70 to 80g every 8 weeks with subsequent improvement of GS, RODS, SF-36, and eMRC sumscoreSS. Patient P16 deteriorated after reducing had been initially the treated with oneIVIg loading IVIg dose of 2g/kg (140g) to the followed by a maintenance monthly dose of 1g/kg (70g) every month. Clinical deterioration was noted after switching to the maintenance dose. In this patient, the dose of IVIg was progressively increased to 120g with subsequent improvement of GS, RODS, SF-36, and eMRC sumscoreSS.

SClinical utility ofensitivity of different assessment outcome measures in adjusting IVIg therapyand their MCID cutoffs

We assessed the sensitivity of four different GS MCID thresholdsdifferent MCID for GS (8, 10, 12 and 14 kPa), one forfor detecting clinically significant change in individual patients. We rejected the following criteria because of insufficient specificity: ≥8 kPa, ≥ 10 kPa, ≥ 12 kPa, and ≥ 14 kPa for one day, and selected the following criteria for the analysis: ≥8 kPa, ≥ 10 kPa, ≥ 12 kPa, and ≥ 14 kPa for at least four consecutive days. Each GS criterion was compared against RODS and three three criteria ffor the eMRC sumscoreSS (≥ 2 points, ≥ 3 points, and ≥ 4 points) (full data results for each patient shown in supplementary table 3). Table 3 summarizes the sensitivity of each of these criteriaand compared their sensitivity with against subjective improvement (table 3).

Among the 15 patients who improved or deteriorated during the adjustment of IVIg dose, a clinically significant change was objectively confirmed by the eMRC sumscore eMRCSS in 14 (93%) patients using with a ≥ 2 points as MCID ccutoff, in 8 (53%) patients withusing ≥ 3 points, and in 4 (27%) patients forusing ≥ 4 points;. This was observed by RODS in 11 (73%) patients, and by GS in 8 (53%) patients with no difference among among tthe different MCID criteria for GS.. None of the outcome measures alone was sufficient to detect clinically significant changes in all patients. Clinical change was confirmed by all three outcome measures in five (33%) patients, by two outcome measures by all the three outcome measures together, in eight (53%) patients by two outcome measures, and by one measure in two (13%) patients by only one outcome measure. Each criterion showed very good agreement with patients' self-reported change in general health, with the only exception of GS ≥ 8 kPa and ≥ 10 kPa for at least four consecutive days for four days. Since clinically relevant change in our patients was not confirmed simultaneously by GS, RODS and eMRCSS (supplementary table 3),When we assessed the timing of the change in each measure, we found that the e we assessed sensitivity to detect earlyiest change considering only the first outcome measure that had detected the change. Early sensitivity were was greatest for RODS

(73%), and ~~followed by~~ GS (53%) with no significant difference between the ~~atwo among the different criteria~~, then ~~and by~~for eMRC sumscore~~SS~~ (27%) (Table 3).

There were some differences in the detection of clinical changes in patients with CIDP and MMN

~~We also evaluated sensitivity of each criterion analyzing CIDP and MMN patients separately~~. In CIDP patients, clinically change were detected by RODS in 7 (100%) patients, by ≥ 2 points in eMRC sumscore in 6 (86%), and by GS in 2 (29%) patients. In all ~~the~~ MMN patients~~group~~, clinically significant change was ~~objectively~~ confirmed by ≥2 points in eMRC sumscore~~eMRCSS using '≥ 2 points' criterion in 8 (100%), using '≥ 3 points' criterion in 5 (62%), using '≥ 4 points' criterion in 3 (37%),, by GS in 6 (75%) by GS~~ and by RODS in ~~6~~ 4 (~~7~~50%)~~, , and by RODS in 4 (50%) patients. In the CIDP group, clinically relevant change was detected by RODS in 7 (100%) patients, by eMRCSS using '≥ 2 points' criterion in 6 (86%) patients, using '≥ 3 points' criterion in 3 (43%) patients, using '≥ 4 points' criterion' in 2 (29%) patients, and by GS in 2 (29%) patients.~~ Early clinical change were also different in the two groups. In CIDP patients, early change was detected by RODS in 7 (100%) patients, ~~by~~ GS in 2 (29%), and by ~~eMRCSS using '~~≥ 2 points eMRC sumscore~~' criterion~~ in 2 (29%)~~ patients, and using '≥ 3 points' and '≥ 4 points' criterion in one (14%) patient, respectively~~. ~~I~~In MMN patients early change were found~~, early change was detected~~ by GS in 6 (75%) patients, by RODS in 3 (37%) patients, by ≥ 2 points eMRC sumscore ~~eMRCSS using '≥ 2 points' criterion~~ in 2 (25%) patients, and using '≥ 3 points' criterion in 1 (12%) patient. In CIDP patients, early change was detected by RODS in 7 (100%) patients, by GS in 2 (29%), by eMRCSS using '≥ 2 points' criterion in 2 (29%) patients, and using '≥ 3 points' and '≥ 4 points' criterion in one (14%) patient, respectively.

Of the four patients in whom IVIg treatment was suspended without objective clinical worsening, two (~~P~~10, ~~P~~11) had a transient fluctuation of RODS score and one (~~P~~19) a transient

fluctuation of the ~~eMRCSS~~eMRC sumscore that were not associated with subjective impression of health ~~change~~ change.~~and thus were interpreted as random fluctuations.~~

~~Role of the~~ H~~h~~ome measurement of GS and RODS to assess end-of dose effect~~monitoring of outcome measures~~

We evaluated the ability of ~~the frequent~~ home monitoring of outcome measures between IVIg cycles to evaluate end-of dose effect of IVIg therapy and predict response to subsequent ~~IVIg~~ dose adjustment. A ~~We tested the hypothesis that clinically significant IVIg-related fluctuation is a marker of IVIg treatment dependency in the individual patient. We dichotomized patients in two groups: 1) patients with S~~subjective end-of-dose effect during the baseline assessment was observed by SF-36 in eight patients and was confirmed in all by ~~IVIg-related fluctuation of~~ GS (3 patients),~~or~~ RODS (3 patients) or both (two patients)~~was present in 8 (40%) patients (P2, P8, P9, P12, P15-P18) at baseline, of whom in 3 confirmed by GS alone (P15, P17, P18), in 3 confirmed by RODS alone (P2, P8, P9), and in 2 by both.~~ ~~-~~All these patients had ~~C~~clinically significant ~~change~~improvement confirmed by GS or RODS after IVIg increase or worsening after its reduction. Only ~~dose adjustment occurred in all of these clinically significant IVIg-related fluctuations of SF-36 confirmed by GS or RODS at baseline and 2) patients without. Then, we calculated the proportion of patients with significant clinical change after IVIg dose adjustment in each group. Subjective end-of-dose effect confirmed by IVIg-related fluctuation of GS or RODS was present in 8 (40%) patients (P2, P8, P9, P12, P15-P18) at baseline, of whom in 3 confirmed by GS alone (P15, P17, P18), in 3 confirmed by RODS alone (P2, P8, P9), and in 2 by both. Clinically significant change after IVIg dose adjustment occurred in all of these patients compared to~~seven of the ~~only 7 (58%) of the~~ 12 patients (58%) without IVIg-related fluctuation had a clinical variation upon dose modification.

Discussion

Our study shows that the frequent monitoring of a set of outcome measures may provide useful information to objectively confirm response to IVIg treatment adjustment in the individual patient with CIN. Despite its common use in clinical trials, our study shows that the MCID cutoff of 8 kPa cannot reliably distinguish clinically significant change from random fluctuations in the individual patient. Specificity has not sufficiently improved by using stricter criteria, as 10kPa, 12kPa or 14 kPa for one day. A recent study showed that random fluctuations of GS exceeded 8 kPa in 27-33% of patients with CINs and proposed a threshold of ≥8 kPa for three consecutive measured days using raw data or 5-day block mean using smoothed data in the individual patient (11). Since smoothing the data requires a time-consuming analysis, in our study we developed simpler criteria for use in clinical practice. These criteria were chosen based on the assumption that clinically significant change, unlike random fluctuation, remains consistent for several days. We demonstrated that using the same threshold values for a minimum of four consecutive days increased specificity of the criteria up to acceptable levels (77-90%) for their use in the individual patient. Compared with *maximum* GS value, *mean* daily GS had slightly smaller 'random' fluctuations so was more specific. Since the GS criterion of '14 kPa on at least four consecutive days' had the same sensitivity (53%) as the other criteria but greater specificity (90%) and better agreement with patients' self-reported change in general health (92%), we recommend its use as more specific indicator of clinically significant change in an individual.

No significant training effect of GS was found in healthy controls after a month of practice. Almost 50% of the healthy controls in our study had reduced GS in at least one hand compared with normal reference values (16) despite not having any medical condition affecting their GS. This suggests that the reliability of these criteria is questionable.

Although GS has been shown to be a sensitive tool (9), our study shows that it has lower ability to detect change compared to RODS and eMRCSS. This may possibly be explained by the fact that GS measures only distal upper-limb strength and thus is not able to capture proximal weakness,

sensory impairment and deficits in the lower limbs (17). Its overall sensitivity was indeed very low in CIDP (29%) but not in MMN (75%). eMRCSS using '≥ 2 points criterion' showed the overall greatest sensitivity. Although this criterion was not validated for this version of the MRC sumscore, it showed a very good agreement with patients' own judgment of change in their global health (93%), and its sensitivity was greater than that of the other eMRCSS criteria. Sensitivity of the eMRCSS was greater than that of RODS in MMN but not in CIDP patients, possibly because in this latter group some activity limitation was secondary to sensory impairment. At the other end of the spectrum, however, eMRCSS showed a lower ability to detect early change compared to GS and RODS. Also in this aspect, GS showed a greater sensitivity in MMN than in CIDP, where RODS more frequently detected early changes. Our study was not designed to evaluate specificity of the MCID thresholds for RODS and MRC sumscore. However, we demonstrated the presence of random fluctuations of RODS and eMRCSS in some of our patients. Future studies should investigate the specificity of MCID criteria for RODS and eMRCSS to define clinically relevant change in an individual. None of the outcome measures alone was sufficient to detect clinically significant changes in all patients and importantly clinical change was detected by at least two outcome measures in most of the patients, suggesting that a multimodal approach using GS, RODS, and eMRCSS should be preferred for the assessment of the individual patient.

Our study also suggests that the frequent monitoring of outcome measures might be useful to predict response to IVIg treatment adjustment in the individual patient with CIN. This information cannot be obtained by fixed-point observation, such as outpatient visits to hospital. Significant clinical change occurred in all patients with a subjective end-of-dose effect confirmed by GS or RODS suggesting that demonstration of objective IVIg-related fluctuation might be a good indicator of treatment dependency in the individual patient. Clinical change, instead, occurred only in some patients without objective IVIg-related fluctuation suggesting that this group is heterogeneous and inclusive of patients with optimum individualization of dosing or excessive treatment and patients having gone into remission. If these findings will confirmed by prospective

studies on a large cohort of patients, this could be applied to identify treatment dependent patients to enroll in clinical trials, avoiding the current practice of IVIg dose reduction trial and making recruitment more attractive for patients and investigators (18). Moreover, this could be useful to guide the individualization of IVIg therapy in routine clinical practice.

Limitations of our study include the small number of patients, heterogeneity of disease state, and brief data collection period. Future studies should evaluate the possible role of frequent assessment of outcome measures as biomarker of IVIg treatment dependency and address long-term consequences of treatment related clinical fluctuations.

In conclusion, the home monitoring of outcome measures provides useful information to assist clinical decision on adjustment of IVIg treatment and seems to predict its response in the individual patient. We recommend a multimodal approach using different outcome measures to monitor the individual patient with CIN and suggest the most clinically appropriate criteria of ’14 kPa for at least four consecutive days’ for GS and ≥ 2 points for the eMRCSS to define clinically relevant change in an individual.

References

1. Elovaara I, Apostolski S, van Doorn P, Gilhus NE, Hietaharju A, Honkaniemi J, et al; EFNS. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases: EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases. Eur J Neurol 2008; 15:893-908.

2. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society--first revision. J Peripher Nerv Syst 2010; 15:295-301.

3. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society First Revision. J Peripher Nerv Syst 2010; 15:1-9.

4. IVIg Guideline Development Group of the IVIg Expert Working Group. Clinical Guidelines for Immunoglobulin Use, 2nd Edn. Department of Health 2012.

5. Patwa HS, Chaudhry V, Katzberg H, Rae-Grant AD, So YT. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2012; 78:1009-1015.

6. Lunn MP, Ellis L, Hadden RD, Rajabally YA, Winer JB, Reilly MM. A proposed dosing algorithm for the individualized dosing of human immunoglobulin in chronic inflammatory neuropathies. J Peripher Nerv Syst 2016; 21:33-37.

7. Rajabally YA. Long-term immunoglobulin therapy for chronic inflammatory demyelinating polyradiculoneuropathy. Muscle Nerve 2015; 51:657-661.

8. Doneddu PE, Nobile-Orazio E. Management of chronic inflammatory demyelinating polyradiculopathy. Curr Opin Neurol. 2018 Oct;31(5):511-516.

9. Vanhoutte EK, Latov N, Deng C, Hanna K, Hughes RA, Bril V, et al. Vigorimeter grip strength in CIDP: a responsive tool that rapidly measures the effect of IVIG--the ICE study. Eur J Neurol 2013; 20:748-755.

10. Merkies IS, van Nes SI, Hanna K, Hughes RA, Deng C. Confirming the efficacy of intravenous immunoglobulin in CIDP through minimum clinically important differences: shifting from statistical significance to clinical relevance. J Neurol Neurosurg Psychiatry

2010; 81:1194-1199.

11. DONEDDU, HADDEN, 2020 (da inserire)

12. van Schaik IN, van Geloven N, Bril V, Hartung HP, Lewis RA, Sobue G, et al; PATH study group. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (The PATH Study): study protocol for a randomized controlled trial. Trials 2016; 17: 345.

13. American Society of Hand Therapists. Chicago IL: Clinical Assessment Recommendations, 2nd edn; 1992. 43 p.

14. Van Nes SI, Vanhoutte EK, van Doorn PA Hermans M, Bakkers M, Kuitwaard K, et al. Rasch-built Overall Disability Scale (R-ODS) for immune-mediated peripheral neuropathies. Neurology 2011; 76:337-345.

15. Vanhoutte EK, Faber CG, van Nes SI, Cats EA, Van der Pol WL, Gorson KC, et al; PeriNomS Study Group. Rasch-built Overall Disability Scale for Multifocal motor neuropathy (MMN-RODS). J Peripher Nerv Syst 2015; 20: 296-305.

16. Merkies IS, Schmitz PI, Samijn JP, Meché FG, Toyka KV, van Doorn PA. Assessing grip strength in healthy individuals and patients with immune-mediated polyneuropathies. Muscle Nerve 2000; 23:1393-1401.

17. Knak KL, Andersen LK, Christiansen I, Markvardsen LK. Does grip strength reflect isokinetic muscle strength in lower limbs in patients with chronic inflammatory demyelinating polyneuropathy? Muscle Nerve 2018; 58:449-452.

18. Hughes R, Dalakas MC, Merkies I, Latov N, Léger JM, Nobile-Orazio E, et al; FORCIDP Trial Investigators. Oral fingolimod for chronic inflammatory demyelinating polyradiculoneuropathy (FORCIDP Trial): a double-blind, multicentre, randomised controlled trial. Lancet Neurol. 2018 Aug;17(8):689-698.