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CLINICAL RESEARCH ARTICLE

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Assessment timing and choice of outcome measure in determining treatment response in chronic inflammatory demyelinating polyneuropathy: A post hoc analysis of the PRISM trial

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Abstract

Introduction/Aims: Treatment response and its timing are variable in chronic inflammatory demyelinating polyneuropathy (CIDP). In this study we assessed the variability using multiple outcome measures.

Methods: We performed a post hoc analysis of the PRISM trial, a 24-week prospective, multicenter, single-arm, open-label, phase III study of a 10% intravenous immunoglobulin preparation for CIDP. We ascertained timing of response with primary/secondary outcome measures.

Results: At 6 weeks after treatment initiation, 13 of 40 subjects (32.5%) were defined as responders on the primary outcome measure, the adjusted Inflammatory Neuropathy Cause And Treatment (INCAT) scale. This increased to 20 of 41 (48.8%) at 12 weeks and to 32 of 42 (76.2%) at 24 weeks. Use of minimal important difference (MID)-determined amelioration of the inflammatory Rasch-built Overall Disability Scale (I-RODS), or of the Medical Research Council sum score (MRCSS), or of dominant hand-grip strength, in addition to the adjusted INCAT, indicated a sensitivity of 41.7% in identifying adjusted INCAT nonresponders at week 12 who subsequently responded at week 24. Specificity was 60% vs INCAT nonresponders at week 24. Consideration of amelioration of any amplitude on any secondary outcome measure indicated a 75% sensitivity, but only 30% specificity vs adjusted INCAT nonresponders at week 24.

Discussion: Immunoglobulin treatment continuation may be justified for up to 24 weeks in CIDP. Additional outcome measures may help in the early treatment stages to predict delayed response on the adjusted INCAT. However, their use is limited by high false-positive rates. More robust, reliable, and relevant outcome measures are needed to detect early improvement in immunoglobulin-treated CIDP.

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; EOS, end of study; ICE, Immune Globulin Intravenous CIDP Efficacy; INCAT, Inflammatory Neuropathy Cause And Treatment; I-RODS, Inflammatory Rasch-built Overall Disability Scale; IVIg, intravenous immunoglobulin; MID, minimum important difference; MRCSS, Medical Research Council sum score; PRIMA, Efficacy and safety of Privigen in CIDP; PRISM, International Multicenter Efficacy and Safety study of Iqumune in initial and maintenence treatment in CIDP.

KEYWORDS
chronic inflammatory demyelinating polyneuropathy, immunoglobulins, outcome measures, response, treatment

1 | INTRODUCTION

Intravenous immunoglobulin (IVIg) has been shown to be efficacious for chronic inflammatory demyelinating polyneuropathy (CIDP) in the short and long term.[1] In a recently published international, multicenter, prospective, single-arm study International Multicenter Efficacy and Safety study of Iqumune in initial and maintanence treatment in CIDP (PRISM), the efficacy of a 10% intravenous preparation of normal human immunoglobulin was demonstrated, compared with a historical control group from a previous trial.[2] The adjusted Inflammatory Neuropathy Cause And Treatment (INCAT) scale was used as primary outcome measure. Favorable effects were also demonstrated on secondary outcome measures, including the Inflammatory Rasch-built Overall Disability Scale (I-RODS), the Medical Research Council sum score (MRCSS), and grip strength.

Although favorable treatment effects were confirmed at 24 weeks, the timing of the therapeutic response was variable from one patient to another. This is of importance because the duration of a treatment attempt with immunoglobulins for CIDP is often 8 to 10 weeks in clinical practice.[3] Furthermore, despite demonstrated favorable effects on secondary outcomes in the PRISM trial and others, the benefit of use of these scales in identifying responders remains unknown, particularly in relation to the timing of assessment.

The timing and outcome measure(s) used to ascertain treatment response are of vital importance in CIDP.[4] In clinical practice, these factors impact directly on the length of time a treatment may be tried before it is considered ineffective. In case of perceived ineffectiveness, a switch to an alternative therapy is then considered. With regard to IVIg, recent published algorithms suggest two courses of treatment with IVIg at a dose of 2 g/kg, at a 3- to 4-week interval, with assessments 8 to 10 weeks after treatment initiation.[3,5] In the absence of a detectable response at that stage, immunoglobulins are generally considered ineffective. Other treatment modalities exist but may raise similar questions in relation to the duration of a treatment trial.[6] The use of variable outcome measures and the lack of generalized application of minimum important difference (MID)-based cut-offs substantially compound the difficulties and complexities of clinical management of subjects with CIDP started on immunoglobulins. The adjusted INCAT (or equivalents, such as the overall neuropathy disability scale[7]), used in the PRISM trial and other previous trials, is not systematically utilized in clinical practice. Other published outcome measures are sometimes preferred. These may include the I-RODS, which is believed to assess a wider range of disabilities[8]; grip strength, which has been shown to correlate with disability levels[9,10]; and MRCSS, which, despite its known limitations, remains very widely used. Available MID cut-offs are not systematically applied, leaving the interpretation of measured changes to the discretion of physicians, and sometimes patients themselves.[11]

In this investigation, we performed a post hoc analysis of the PRISM trial data to ascertain response amplitudes and proportions of responders at various time-points during the study. Our main objective was to establish comparative gains in identification of additional treatment responders at progressing study time-points.

2 | METHODS

The PRISM study was a phase III, international multicenter, single-arm, open-label, prospective trial of the safety and efficacy of a 10% intravenous preparation of normal human IVIg (IqYmune; LFB, Les

TABLE 1 Responder numbers, proportions, and change at assessment time-points on adjusted INCAT[a] scale over the course of the International Multicenter Efficacy and Safety study of Iqumune in initial and maintanence treatment in CIDP trial

Timing of assessment	Total cumulative number of responders at time-point	Cumulative percentage of responders at this time-point in relation to total number of responders at EOS[b] (32 subjects)	Percentage of additional responders over previous 3 weeks in relation to total number of responders at EOS (32 subjects
Week 3 (before second course)	7	21.9%	21.9%
Week 6 (before third course)	13	40.6%	18.8%
Week 9 (before fourth course)	18	56.3%	15.6%
Week 12 (before fifth course)	20	62.5%	6.3%
Week 15 (before sixth course)	23	71.9%	9.4%
Week 18 (before seventh course)	27	84.4%	12.5%
Week 21 (before eighth course)	30	93.8%	9.4%
Week 24 (after eighth course)—EOS	32	100%	6.3%

EOS, end of study; INCAT, adjusted inflammatory neuropathy cause and treatment.

Ulis, France) for patients with CIDP [2]. This study, approved by local independent ethics committees, was registered at ClinicalTrials.gov (NCT02293460) and EudraCT (2013–005557-73). Details of patient selection and recruitment as well as product administration, were described in detail in earlier work.[2] In summary, IVIg was administered at an initial dose of 2 g/kg over 2 to 5 days during the first course, then maintenance doses of 1 g/kg over 1 to 2 days repeated every 3 weeks (±7 days) during the seven subsequent courses.

PRISM study evaluations with the primary outcome measure, adjusted INCAT, were performed at 3-weekly intervals between the pretreatment assessment and the end of study (EOS). We evaluated the proportion of responders at weeks 3, 6, 9, 12, 15, 18, 21, and 24. The increase in number of identified responders was determined for each visit and compared with the previous visit and the pretreatment visit. The MRCSS, I-RODS, and dominant hand-grip strength were evaluated, as per the study protocol, at the pretreatment visit, week 12, and week 24. We considered responder status with each of these scales according to published literature using the MID cut-offs for each. This was 4 points for the raw I-RODS score,[12] 4 points for the MRCSS,[12] and 8 kPa for grip strength.[9]

TABLE 2 Responder rates with each of four outcome measures used at week 12 and EOS

	Week 12	EOS
Adjusted INCAT	20 of 41 (48.8%)	32 of 42 (76.2%)
I-RODS score	17 of 39 (43.6%)	21 of 42 (50%)
MRCSS	15 of 39 (38.5%)	17 of 41 (41.5%)
Dominant hand-grip strength	16 of 40 (40.0%)	17 of 41 (41.5%)

EOS, end of study; INCAT, adjusted inflammatory neuropathy cause and treatment; I-RODS, Inflammatory Rasch-built Overall Disability Scale; MRCSS, Medical Research Council sum score.

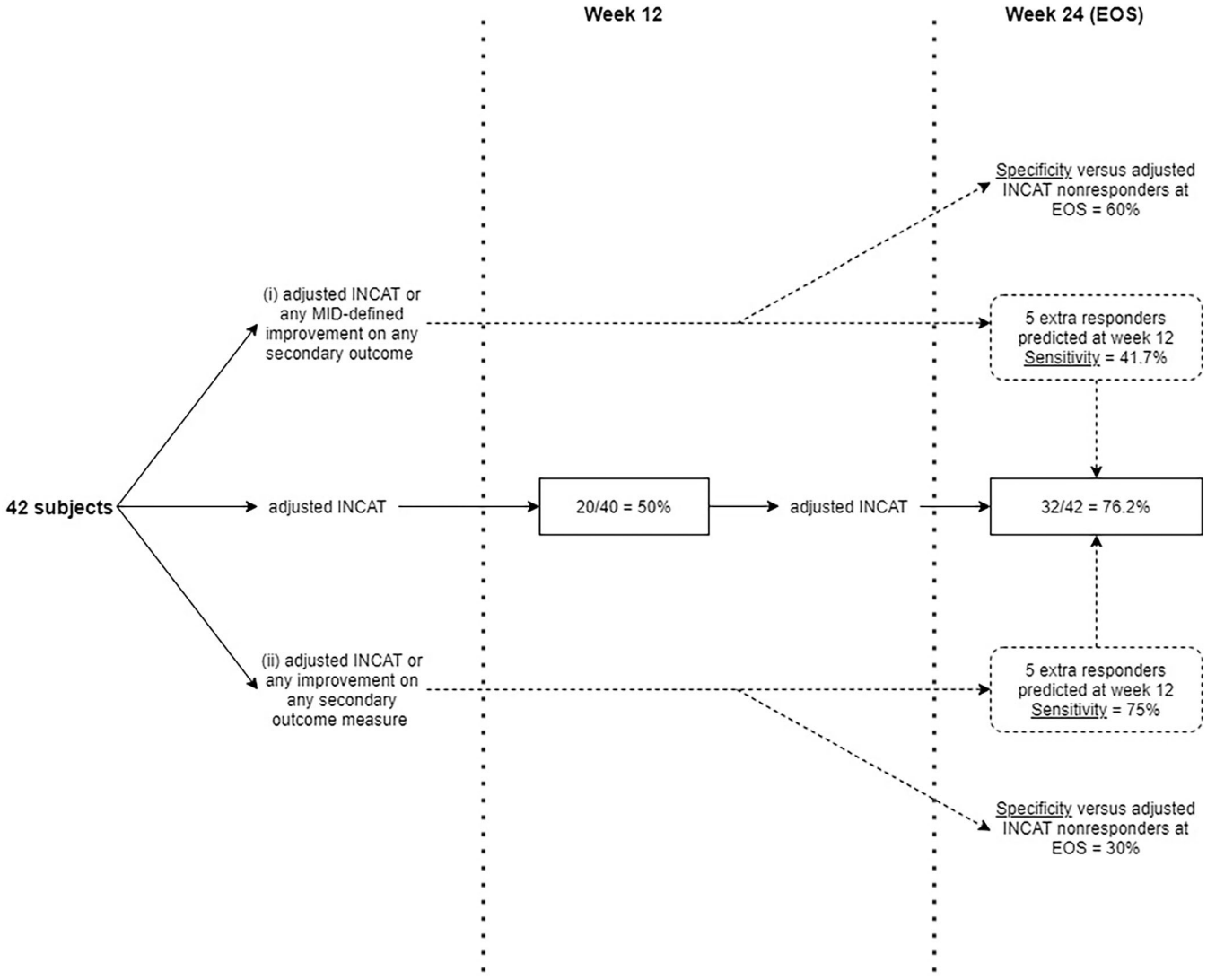

FIGURE 1 Early prediction of treatment response. Use of combination of secondary outcome measures to recognize at week 12, adjusted inflammatory neuropathy cause and treatment (INCAT) nonresponders who subsequently responded by end of study (EOS) when considering (i) minimum important difference (MID)-defined improvement of any secondary outcome measure and (ii) any degree of improvement of any secondary outcome measure. Note also that 40 of 42 subjects were evaluated by adjusted INCAT at week 12, whereas 42 of 42 were evaluated at EOS. The two subjects not evaluated at week 12 were both responders on the adjusted INCAT at EOS.

Similarly, the increase in number of responders was determined at week 12 and week 24 and compared with the previous time-point and/or to the pretreatment visit, as were the differences between the corresponding mean recorded changes for each scale. The aforementioned analyses were performed in the full analysis set (FAS).

We used the same methods as those used in the initial trial report, with the last observation carried forward to establish responder rates for each outcome measure.

3 | RESULTS

A progressive increase was found in the number of responders identified using the adjusted INCAT scale between week 3 and EOS (Table 1). A progressive increase in proportions of responders was observed between week 3 and EOS. Notably, 16 of 23 (69.6%) immunoglobulin-naive subjects improved on the adjusted INCAT by the EOS as compared with 16 of 19 (84.2%) pretreated subjects ($P = .30$).

Responder status defined by MID cut-offs for the secondary outcome measures as well as adjusted INCAT are summarized in Table 2. At week 12, responder rates for the three secondary outcome measures were not superior to that of the adjusted INCAT. At EOS, none of the three secondary outcome measures demonstrated superior responder rates when compared with adjusted INCAT.

We attempted to determine the usefulness of early changes on the secondary outcome measures in predicting response on the adjusted INCAT at EOS. The results are summarized in Figure 1. Of the 12 subjects who responded on the adjusted INCAT between week 12 and EOS, 5 (sensitivity = 41.7%) showed a MID-defined response on one or more secondary outcome measure already at week 12. In addition, 4 of the 12 subjects (33.3%) had displayed sub-MID improvement on any of the secondary outcomes at week 12. Hence, 9 of the 12 (sensitivity = 75%) delayed adjusted INCAT responders, who became responders between week 12 and EOS showed an improvement of any amplitude on at least one secondary outcome measure already at week 12.

However, the specificity of MID-defined improvement at week 12 on any secondary outcome measure vs adjusted INCAT nonresponders at week 24 was 6 of 10, or 60%. The specificity of any improvement on any secondary outcome measure vs adjusted INCAT nonresponders at week 24 was 3 of 10, or 30%. Finally, discrepant results amongst the secondary outcome measures (any improvement on at least one and any deterioration on at least one) were present at week 12, in 4 of 10 (40%) of the INCAT nonresponders at EOS.

4 | DISCUSSION

Detailed results of the PRISM trial have been described previously.[2] In summary, and with direct relevance to the current post hoc analysis, the overall response rate at EOS using the adjusted INCAT scale was 32 of 42, or 76.2% (95% confidence interval, 60.5% to 87.9%). The median change in adjusted INCAT score was −1 point at EOS (95% confidence interval, −1.5 to −1.0; $P < .001$). There were significant changes at EOS for mean I-RODS score (4.0; standard deviation [SD], 8.5; $P = .0036$), mean MRCSS (3.48; SD, 5.8; $P = .0001$), and mean dominant hand-grip strength (12.0; SD, 26.9; $P = .0076$).

These post hoc study findings suggest the possible inadequacy of 8- to 10-week immunoglobulin treatment trials for CIDP. Between week 6 and week 24, 19 subjects responded on the adjusted INCAT, in addition to the 13 responders at week 6, thus amounting to an increase of almost 150% in absolute numbers. Importantly, the delay in response was more marked in immunoglobulin-naive subjects,[2] which is typical in clinical practice. Second, we found that the I-RODS, MRCSS, and dominant grip were not superior to the adjusted INCAT for identifying responders using MID-defined cut-offs at week 12 or EOS.

We found that the secondary outcome measures detected early changes that may be predictors of a delayed response in the adjusted INCAT. This finding is useful for clinical practice, as it suggests that these changes may predict patients who may require longer duration treatment. However, the specificity of the combined use of secondary outcomes at week 12 was poor and discrepant results were common. Thus, there may be a potential for these outcomes in early disease, but our results highlight their inadequacy and the contradictory changes observed on the different scales. There is a need for more research on meaningful measurement of change in CIDP.

In the Immune Globulin Intravenous CIDP Efficacy (ICE) study,[1] a randomized, double-blind, placebo-controlled, response-conditional crossover trial of another immunoglobulin product for CIDP, an unchanged adjusted INCAT at week 6 in the first period resulted in crossover, preventing direct comparative analyses with the current post hoc study. However, four subjects randomized to the immunoglobulin arm continued immunoglobulin treatment instead of being crossed over at week 6 and improved and maintained improvement to week 24. Thus, 4 of 32 (12.5%) responders in the ICE study improved after week 6, with an unspecified additional percentage having possibly improved between week 3 and week 6. The ICE study included 32 of 117 (27.4%) pretreated participants, amongst whom 20 of 32 (60%) responded to immunoglobulin in the first period, compared with 20 of 39 (51.3%) immunoglobulin-naive subjects; these are comparable responder rates to those observed in the PRISM study.

In the PRIMA study,[13] a single-arm, open-label, phase III study of another immunoglobulin product in Efficacy and Safety of Privigen in CIDP (CIDP), a gradual increase in the proportion of responders on the adjusted INCAT also was observed. At week 4, there were 9 of 28 (32.1%) responders, increasing to 14 of 28 (50%) at week 7, 16 of 28 (57.1%), at week 10, and 18 of 28 (64.3%) at week 19. Participants were pretreated or immunoglobulin-naive in similar proportions in the PRIMA study (46.4% vs 53.6%, respectively) and the PRISM study (45.2% vs 54.8%, respectively), and the responder rates in both groups were comparable in the two studies (8 to 15 vs 16 to 23 and 10 to 13 vs 16 to 19, respectively).

Conversely, however, the Progress in Chronic Inflammatory Demyelinating Polyneuropathy (ProCID) study,[14] a multicenter, randomized, prospective, double-blind, dose-comparative, parallel-group study of another immunoglobulin product in CIDP, demonstrated a 50.7% response rate after induction at 2 g/kg of immunoglobulin at week 3, increasing to 80% at week 6, with a single further maintenance immunoglobulin dose of 1 g/kg. The ProCID study allowed immunoglobulin continuation during the washout period up to inclusion, with 12 participants still being on immunoglobulin at inclusion. The ICE, PRIMA, and PRISM studies, in contrast, excluded immunoglobulin use in the 3 months before inclusion. Furthermore, 87% of subjects in the 1-g/kg dose group of the ProCID study were pretreated with corticosteroids, with 33% still on no more than 20 mg/day of corticosteroids at time of inclusion. A maximum dose of 10 mg/day corticosteroids was authorized in the ICE study, with no concomitant steroids allowed during washout, in the PRIMA and PRISM studies. Therefore, it is possible immunoglobulin and/or corticosteroid therapy before inclusion influenced the timing of response in the ProCID study.

The latest updated guidelines for CIDP from the European Academy of Neurology and Peripheral Nerve Society recommend the use of one disability (adjusted INCAT or I-RODS) and one impairment (MRCSS or grip strength) measure to assess response.[15] It is uncertain if and how this may aid in evaluation of treatment effects in view of the known limitations of the Medical Research Council scale,[16] as well as doubts about how to optimally consider grip-strength ameliorations, between absolute value[10] or percent change.[17]

Our study has limitations. The number of patients studied was relatively small. This post hoc work was not powered for the further analyses performed. Hence, our findings are descriptive with no attempt at evaluating statistical significance. The secondary outcome measures were applied before treatment initiation, at week 12, and at EOS only, whereas the adjusted INCAT was targeted for evaluation every 3 weeks. It remains uncertain why the adjusted INCAT responder rate gradually improved while other measures plateaued by week 12. For strength measures (MRCSS and grip), it is possible that, after early plateauing, further but slower improvement, particularly of proprioceptive function, allowed subsequent functional improvement, as measured on the adjusted INCAT. The early plateauing of the I-RODS score may relate to possible inadequacy of a standard MID cut-off of 4 points, irrespective of baseline, or to issues directly related to the scale's validity in the setting of the heterogeneity of CIDP.[18] The CIDP population studied was heterogeneous in relation to disease duration and subtype and further subanalyses were not possible. Furthermore, these would have been limited by small numbers. Also, the study population comprised a substantial proportion of immunoglobulin-pretreated subjects, which may have impacted on the findings. Finally, it is noteworthy that the findings of this post hoc study relate exclusively to immunoglobulin treatment of CIDP.

Despite these limitations, the results of our post hoc analysis suggest that the question of the duration of a trial of treatment with immunoglobulins may need to be revisited in CIDP. The data show that the I-RODS, MRCSS, and dominant hand-grip strength assessments may be helpful in early treatment stages to recognize early response, but the findings may also highlight the poor specificity of changes with these scales and the frequent interscale discrepancies. These findings may have practical implications in the clinical management of subjects with CIDP. Further research is warranted in de novo subjects with CIDP to determine the parameters influencing the timing of response and the optimal assessment methods, particularly in relation to disease subtype, exposure to previous therapies, and other potential confounders.

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CONFLICTS OF INTEREST

None declared.

ETHICS STATEMENT

The PRISM study was approved by local ethics committees in all participating countries.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

Data subject to third party restrictions

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