Summary

Objective > To assess the efficacy and safety of intravenous immunoglobulin (IV Ig) in patients with chronic inflammatory demyelinating polyneuropathy (CIDP) at 4, 7 and 12 months.

Methods > A national multicenter retrospective study was conducted by LFB Biotechnologies in patients with CIDP who had received at least one cycle of a 5% polyvalent IV Ig, Tegeline®, from LFB biomédicaments between 1995 and 2004. The primary endpoint was the efficacy of IV Ig at 4 months, which was defined as the responder rate based on the modified Rankin scale. Several secondary endpoints were assessed: safety and efficacy (i.e., responders according to the investigators’ overall assessment of the patients’ status) at 4, 7 and 12 months. The analysis was performed at 7 months only (due to missing data for 12 months and few patients).

Results > A total of 26 patients were included who had received between 1 and 6 cycles of IV Ig (mean 3 ± 2) with a median follow-up of 9.9 months. The responder rate at 4 months based on the modified Rankin scale was 52% (95% CI 0.313–0.722), whereas the responder rate with placebo reported in the literature (meta-analysis including results from van Schaik and an ICE study) is 18% (P < 0.001). Responder patients at 4 months were still responders at 7 months. The overall safety of IV Ig was good, with adverse events of mild to moderate severity, which resolved without sequelae and were expected adverse events of IV Ig.

Conclusion > This retrospective study confirmed both the efficacy of IV Ig at 4 months in the treatment of chronic inflammatory demyelinating polyneuropathy and the favorable safety profile of the product.
Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) accounts for 10 to 20% of all chronic polyneuropathies [1]. Despite its low prevalence (1 to 7.7 per 100,000) [2-8], CIDP causes disability that is often severe [2,5,7,9]. Classically, the clinical presentation of CIDP is a sensory-motor deficit with a motor predominance that is both distal and proximal and affects all four limbs more or less symmetrically with a gradual onset over the course of more than 2 months. The course is progressive or relapsing in approximately 30 to 60% of cases [2,7,9-12]. In the epidemiological study by Lunn et al. [5], the average disability score for patients at the nadir of CIDP was 3.5 on the modified Rankin scale (table I) [13], and 54% of the patients experienced severe disability at some time in the course of the disease.

Spontaneous remissions, though possible, are highly uncommon, and the disease is relieved or stabilized with immunomodulatory therapy, including corticosteroids, intravenous immunoglobulin (IV Ig) or plasma exchange. The short-term efficacy of these treatments has been demonstrated in placebo-controlled studies, which most frequently involve small numbers of patients [14-19]. The randomized, double-blind ICE study [20], however, included 117 patients and demonstrated the superior efficacy of IV Ig versus placebo at 6 months, which was maintained for an additional 6 months. In a Cochrane systematic review of immunoglobulins [21], IV Ig improved disability for at least two to six weeks compared with placebo, with a risk ratio of 2.4 (95% CI = 1.72-3.36). Few controlled studies have compared the efficacy of IV Ig to corticosteroids or to plasma exchange [22-24], the studies by Hughes et al. [23] and Dyck et al. [22], which involved a small number of patients,
A retrospective study on the efficacy and safety of intravenous immunoglobulin (Tegeline\textsuperscript{®}) in patients with chronic inflammatory demyelinating polyneuropathy

Table 1

Modified Rankin scale by Warlow et al. for the United Kingdom transient ischaemic attack (UK-TIA) study group [13]

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms: able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability: able to look after own affairs without assistance but unable to carry out all previously mentioned activities</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability: requires some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability: unable to attend to own bodily needs without assistance and unable to walk without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability: requires constant nursing care and attention, bed-ridden, incontinent</td>
</tr>
</tbody>
</table>

Methods

We conducted a multicenter retrospective study in five French reference centers for neuromuscular diseases. The study included all patients with CIDP who had received their first administration of a 5\% polyvalent human IV Ig (Tegeline\textsuperscript{®}) (LFB Biomédicaments, France) between January 1, 1995, and December 31, 2004.

Patient enrollment

The investigators selected their patients in the most consecutive and exhaustive manner possible. To this end, the investigators compared the list of patients treated with IV Ig, which was provided by the hospital pharmacy, and the list of CIDP patients who were followed in their department. All files of treated patients who met the inclusion criteria, including the files of lost-to-follow-up or deceased patients, were included to preserve the statistical power of the study and to avoid the introduction of bias related to a lack of completeness.

Eligible patients were over 18 years old with a CIDP diagnosed according to the clinical criteria of CIDP as well as electrophysiological or histological signs of primary demyelination of the Ad Hoc Subcommittee of the American Academy of Neurology of 1991 [25]. These criteria also fulfill European Federation of Neurological Societies (EFNS)/Peripheral Nerve Societies [26] criteria published afterwards in 2005, and who are currently CIDP reference criteria. All enrolled patients gave written consent in 2004–2005 (the beginning of this study). CIDP had been present for at least 6 months prior to study entry, and patients had to be symptomatic with a modified Rankin score of 1 or more (table 1). Purely motor forms of CIDP were accepted. The patients had received at least one cycle of IV Ig and had not been previously treated with another polyvalent human IV Ig. Their clinical neurological status had been stable or worsening prior to the initiation of IV Ig.

The exclusion criteria were severe axonal damage affecting the upper limbs on electroneuromyography (compound muscle action potential at less than 20\% of the lower limit of normal for 2 or more nerves in the upper limbs); pure motor syndrome meeting the diagnostic criteria of motor neuropathy with persistent conduction block [27]; concomitant systemic disease that could cause neuropathy; spontaneous improvement prior to the first cycle of IV Ig; and treatment with corticosteroids, IV Ig, plasma exchange and/or immunosuppressive agents within 6 months prior to study entry. Corticosteroids at a stable dose for at least 3 months and immunosuppressive agents administered for at least 6 months or started at the time of the first cycle of IV Ig were permitted.

This was a non-interventional study that did not require approval from an ethics committee because it did not fall under the Huriet law in France. The French Advisory Committee on Information Processing in Research in the Field of Health (CCTIRS) and the French Commission on Information Technology and Civil Liberty (CNIL) gave favorable opinions on the study protocol on October 27, 2004, and November 4, 2004, respectively.

Treatment

The administered treatment was Tegeline\textsuperscript{®}, a polyvalent intravenous human normal immunoglobulin concentrated at 5\%, freeze-dried, obtained from a pool of healthy subjects and marketed by LFB biomédicaments.

Because this was a retrospective study, no therapeutic regimen could be applied. The administered dose of IV Ig was dependent on the patient’s body weight, usually at 2 g/kg body weight over 3 to 5 days via IV. The cycle of IV Ig could be repeated based on the physician’s assessment and at a frequency decided by him/her, most often at 4-week intervals.

Any treatment that was ongoing or was introduced during the period of evaluation of IV Ig was recorded on the case report form.
Endpoints

The primary endpoint was the responder rate at 4 months. Responders were defined as patients with a reduction of at least 1 point on the modified Rankin scale between the first cycle of IV Ig and the 4-month assessment.

The following secondary efficacy endpoints were assessed:
- the variations in the modified Rankin score at 4, 7 and 12 months, which were calculated as the difference between the Rankin score at 4, 7 or 12 months and the score prior to the first cycle of IV Ig;
- the investigator’s overall assessment of the patient’s status at 4, 7 and 12 months, which was defined by the physician’s evaluation of the effect of each cycle of IV Ig on the patient’s status and included 5 possible responses: “improvement”, “in remission”, “favorable initial response but subsequent aggravation” despite regular infusions of “IV Ig”, “stable” or “deterioration.” Patients considered to be responders were those in the groups “improvement”, “in remission” and “favorable initial response but subsequent aggravation”;
- the responder rate based on the modified Rankin score at 7 and 12 months (same definition as the primary endpoint);
- the safety of IV Ig, assessed by collecting potential adverse events in the files. The nature, severity, duration, frequency and need for corrective measures, if any, were recorded. Adverse reactions were coded using MedDRA and were classified and analyzed according to system-organ class (SOC), preferred term (PT) and lowest level term (LTT).

An additional exploratory analysis was performed to analyze the predictive factors of treatment response at 4 months, as defined in the primary endpoint of the study. Efficacy at 12 months could not be analyzed because of missing data (modified Rankin score data for 5 patients and investigators’ overall assessment for 8 patients).

Statistical analyses

The sample size was calculated on the basis of the expected responder rate with IV Ig (47%) and with placebo (15%), estimated based on a meta-analysis by van Schaik et al. [28]. The ICE study [19], which was published after the meta-analysis, reported two placebo responder rates of 21% and 22% and a responder rate with IV Ig of 56%. Incorporating these data into the meta-analysis by van Schaik, the estimated responder rate (statistical hypothesis) with placebo became 18% and the responder rate with IV Ig became 52%. At least 20 patients had to be included to demonstrate the superiority of IV Ig compared with placebo at 4 months with 90% power and a two-sided α-risk of 5%. The study included 26 patients and therefore had sufficient power to demonstrate the efficacy of IV Ig at 4 months regardless of the rate with placebo.

The statistical analyses were conducted on an intention-to-treat basis, and the significance level (α-risk) was set at 5% (two-sided) for all of the statistical tests used. The variables were expressed, depending on their nature, in terms of frequency, mean, median and standard deviation (SD). For the responder rate, a 95% confidence interval was estimated using an exact binomial distribution. The responder rate was compared to the expected rate with placebo using the Clopper-Pearson test. A univariate analysis and then a multivariate analysis were performed on the predictive factors of treatment response. Only variables with a significance level of P < 0.20 were used for the multivariate analysis with logistic regression using backward elimination.

The analyses were performed with SAS Institute Inc. (Cary, NC, USA) and StatXact-CYTEL® (Cambridge, MA, USA) software.

Results

Number and description of patients and treatment with IV Ig

Among 37 selected patients with CIDP, a total of 26 patients meeting the inclusion and non-inclusion criteria were included in the study and gave their written consent (figure 1). The demographic characteristics of the patients and the history of their disease are presented in table II.

The mean follow-up (± SD) in the study was 9.4 months ± 3.8 (range 2.4-15.9) with a median of 9.9 months.

A total of 72 cycles of IV Ig were collected for the 26 patients. The mean number of cycles (± SD) per patient was 3 (± 2), with a median of 3 and a range from 1 to 6. Patients received a mean dose (± SD) of 1.8 g/kg (± 0.4) of IV Ig per cycle and a median dose of 2 g/kg/cycle (range 0.6-2.3). The mean administered dose was 112.1 g (± 31.3), and the median dose was 112.5 g (range 40-174).

Two patients had concomitant treatment with corticosteroids (a stable dose of corticosteroids initiated prior to the first cycle of IV Ig was permitted during the study): one patient had been treated with prednisolone for 6 months with progressive tapering to reach a stable dose of 15 mg/day 7 weeks prior to the first cycle of IV Ig and discontinuation 13 months after; one patient had been treated with prednisolone for 4 months with progressive tapering to reach a stable dose of 5 mg/day at the time of the first cycle of IV Ig and discontinuation 6 months after. No patients received immunosuppressive agents.

Efficacy analysis

Given the retrospective nature of the study, secondary outcome measures were missing or incomplete in some of the files.

Results at 4 months

All files in which no information was available on the primary endpoints were excluded from the efficacy analysis. The efficacy population at 4 months included 25 patients (figure 1). The responder rate at 4 months for the modified Rankin score was 13/25, i.e., 52% with an exact 95% confidence interval (CI) = [0.313-0.722]. The Rankin score was collected at a mean of 3.03 months ± 1.26, with a range of 0.7-4.7 months (median
3.1 months). Among the 12 non-responders, 9 had a Rankin score that remained unchanged and the 3 others had an increase of more than 1 point.

An analysis of the change in modified Rankin scores at 4 months found a median difference of \(-1\) with a 95% CI of \([-1.5-0.0]\). The change over time between the first cycle of IV Ig and the evaluation at 4 months was statistically significant and in favor of IV Ig (\(P = 0.01\)).

The overall assessment of the patient’s status and of treatment response by the investigator found a responder rate at 4 months of 18/21, i.e., 85.7% (table III). Six patients considered to be non-responders according to the modified Rankin score at 4 months were responders according to the investigators’ overall assessment.

The consistency between the two approaches to efficacy, i.e., Rankin score and investigators’ overall assessment, was compared and evaluated using the kappa coefficient of Cohen. The coefficient was 0.36 for a 95% confidence interval of 0.003–0.70 indicating moderate agreement between the two approaches. Thus, for 15 out of 21 patients, i.e., 71%, the endpoints for the assessment of treatment efficacy were consistent (table IV).

An analysis of the predictive factors of response to IV Ig at 4 months in a univariate analysis and then in a multivariate...
Table II
Demographic characteristics of patients and history of the disease (safety population $n = 26$)

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Total ($n = 26$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) at first cycle of IV Ig (Tegeline®); median (range)</td>
<td>52 (18–80)</td>
</tr>
<tr>
<td>Gender (percentage)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11 (42.3%)</td>
</tr>
<tr>
<td>Male</td>
<td>15 (57.7%)</td>
</tr>
<tr>
<td>Weight (kg); median (range)</td>
<td>61.5 (36.0–96.0)</td>
</tr>
<tr>
<td>Age at onset of first symptoms (years); median (range)</td>
<td>48 (18–77)</td>
</tr>
<tr>
<td>Age at diagnosis (years); median (range)</td>
<td>51 (18–80)</td>
</tr>
<tr>
<td>Time since first symptoms (years); median (range)</td>
<td>1.5 (0.1–19.0)</td>
</tr>
<tr>
<td>Time since diagnosis (months); median (range)</td>
<td>0.7 (–7.4–65.7)</td>
</tr>
<tr>
<td>Timeframe between first symptoms and diagnosis (years); median (range)</td>
<td>1 (0.0–19.0)</td>
</tr>
<tr>
<td>Motor deficit (percentage)</td>
<td>100%</td>
</tr>
<tr>
<td>Distal</td>
<td>92.3%</td>
</tr>
<tr>
<td>Proximal</td>
<td>57.7%</td>
</tr>
<tr>
<td>Symmetrical</td>
<td>73.1%</td>
</tr>
<tr>
<td>Amyotrophy</td>
<td>38.5%</td>
</tr>
<tr>
<td>Sensory deficit (percentage)</td>
<td>80.8%</td>
</tr>
<tr>
<td>Reduced or absent deep tendon reflexes (percentage)</td>
<td>100%</td>
</tr>
<tr>
<td>Forms (percentage)</td>
<td></td>
</tr>
<tr>
<td>Relapsing-remitting</td>
<td>30.8%</td>
</tr>
<tr>
<td>Progressive</td>
<td>69.2%</td>
</tr>
</tbody>
</table>

Table III
Investigator’s overall assessment of patient status at four months (efficacy population at four months, $n = 25$)

<table>
<thead>
<tr>
<th>Patient status</th>
<th>Number of patients (percentage of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-responder (stable status)</td>
<td>3 (14.3)</td>
</tr>
<tr>
<td>Responder</td>
<td>18 (85.7)</td>
</tr>
<tr>
<td>Improvement¹</td>
<td>14 (66.7)¹</td>
</tr>
<tr>
<td>Good initial response before deterioration¹</td>
<td>3 (14.3)¹</td>
</tr>
<tr>
<td>Remission¹</td>
<td>1 (4.8)¹</td>
</tr>
</tbody>
</table>

¹21 instead of 25 (missing data for 4 patients).

Table IV
Consistency between Investigator’s overall assessment of patient status/modified Rankin score at 4 months (efficacy population at 4 months, $n = 25$)

<table>
<thead>
<tr>
<th>Responder/non-responder Rankin 4 months (LOCF)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-responder</td>
<td>3</td>
</tr>
<tr>
<td>Responder</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>21¹</td>
</tr>
</tbody>
</table>

¹21 instead of 25 (missing data for 4 patients).
A retrospective study on the efficacy and safety of intravenous immunoglobulin (Tegeline®) in patients with chronic inflammatory demyelinating polyneuropathy


Results at 7 months

The efficacy population at 7 months (figure 1) included 19 patients. The data on 6 patients were excluded from the efficacy analysis because corticosteroids or plasma exchange (treatments not permitted by the protocol) was initiated between 4 and 7 months. Three of these 6 patients were responders at 4 months and did not have a relapse, but the investigators decided to stop IV Ig and start corticosteroids. Other patients and non-responders at 4 months received plasma exchange followed by corticosteroids.

The population for the efficacy analysis included only 13 patients (data for the modified Rankin score was missing in 6 patients). The responder rate for the modified Rankin score at 7 months was 10/13, i.e., 76.9%, with a 95% CI of [0.462-0.950]. All of the patients who were responders at 4 months for the modified Rankin score were still responders at 7 months, and 8/10 patients who were responders at 7 months were also responders at 4 months according to the modified Rankin score (table V). The overall assessment of the patient’s status and of the treatment response by the investigator found a responder rate at 7 months of 10/11 (data for only 11 patients), i.e., 90.9%.

Safety analysis

During the follow-up period of the study (median 9.9 months; 72 cycles of IV Ig), 10 of the 26 analyzed patients (38.5%) did not experience any adverse events (AEs). Thirty AEs were reported in the remaining 16 patients. Among these, only one AE was reported as a serious adverse event, but this event was not considered to be related to treatment or to the disease (generalized epileptic seizure, which occurred due to the sudden discontinuation of 300 mg oxcarbazepine that had been initiated for paresthesia). All of the other AEs were mild (21 AEs) to moderate (8 AEs) in severity and resolved without sequelae. Table VI shows the AEs, their frequency and their association with IV Ig. Among the 29 non-serious AEs, only 17 (56.7%) were considered to have a probable relationship with treatment. The AEs were mild (11 AEs, i.e., 36.7%) to moderate (6 AEs, i.e., 20%) in severity and involved isolated cases of leucopenia, thrombocytopenia, nausea, vomiting, hyperthermia, dizziness or headache. Neither cases involving kidney failure nor venous or arterial thrombosis were reported. All of the AEs that were considered to be related to IV Ig had already been observed in prior studies in other diseases and were listed in the SmPC. These results confirm the good safety profile of IV Ig (Tegeline®) in the treatment of CIDP at a mean dose of 1.8 g/kg/cycle.

Discussion

We found a responder rate with IV Ig at 4 months for the modified Rankin score of 52%, which confirms its significant therapeutic effect compared with placebo based on historical data from the literature (P < 0.001). Indeed the responder rate with placebo in the literature is of 15% from the van Schaik meta-analysis and of 18% from the meta-analysis including results from van Schaik and the ICE study. This result is consistent with responder rates with IV Ig in double-blind randomized studies reported in the literature, which vary between 43% and 100% [15,17-20,22,29]. The 2 studies in which 100% of the patients were responders were those by van Doorn et al. [29], which included 7 patient responders to IV Ig requiring regular cycles, and Dyck et al. [22], which included 17 patients with severe CIDP. In a meta-analysis involving 113 patients from 4 randomized trials [15,17-19], van Schaik et al. [28] found a responder rate of 47% one month after the first cycle of IV Ig. More recently, the randomized ICE study [20] on IV Ig versus placebo, which included 117 patients, found a responder rate at 6 months of 54% according to the INCAT (improvement in inflammatory neuropathy cause and treatment) Disability Score [23]. The variations in the responder rates with IV Ig in these different studies is most likely due to the differing criteria for patient enrolment and to the scales used to assess the treatment efficacy: Medical Research Council (MRC) score, Neurological Disability Score, Rankin score, modified Rankin score, INCAT Disability Score, INCAT Overall Disability Sum Score (ODSS) [30]. Merkies et al. [31] showed that the INCAT ODSS was the scale that best correlated to the patients’ own assessment of their clinical status regarding CIDP, notably in comparison with the modified Rankin scale. Recently, Panaite et al. (2013) [32]
showed that general disability scores (i.e. Neurological Disability Score, INCAT Disability Score, INCAT ODSS) and motor scores/scales (e.g. MRC score and new Rasch-built overall disability scale [33]) were strongly correlated with CIDP disease activity status contrary to Sensory scores (INCAT Sensory Sum Score [34]). The INCAT ODSS therefore appears to be more appropriate than the modified Rankin scale. This finding can be explained by the fact that the modified Rankin scale is only a 5-point scale,

<table>
<thead>
<tr>
<th>System-organ class/lowest level term</th>
<th>Relatedness</th>
<th>Number of AEs</th>
<th>Number of patients</th>
<th>% of number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>30</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td><strong>Number of patients with at least 1 AE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td>2</td>
<td>1</td>
<td>3.80</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>Likely</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
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<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td>3</td>
<td>3</td>
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<tr>
<td>Nausea</td>
<td>Likely</td>
<td>1</td>
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</tr>
<tr>
<td>Vomiting</td>
<td>Unlikely</td>
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<td>1</td>
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<tr>
<td><strong>General disorders and administration</strong></td>
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<td>3</td>
<td>11.50</td>
</tr>
<tr>
<td><strong>Inflammation at injection site</strong></td>
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<td>1</td>
<td>1</td>
<td></td>
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<tr>
<td>Hyperthermia</td>
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<td>1</td>
<td></td>
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<tr>
<td>Localised oedema</td>
<td>Unlikely</td>
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<td>1</td>
<td></td>
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<tr>
<td><strong>Nervous system disorders</strong></td>
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<td>15</td>
<td>12</td>
<td>46.20</td>
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<tr>
<td>Light-headedness</td>
<td>Possible</td>
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<td>1</td>
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<td></td>
<td>Likely</td>
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<td>1</td>
<td></td>
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<tr>
<td>Epilepsy</td>
<td>Unrelated</td>
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<td>1</td>
<td></td>
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<tr>
<td>Headache</td>
<td>Possible</td>
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<td></td>
<td>Likely</td>
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<td>8</td>
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<td>Paraesthesia</td>
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<td>Insomnia</td>
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<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
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<td>3</td>
<td>11.50</td>
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<tr>
<td>Localised skin reaction</td>
<td>Possible</td>
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<td>Rash</td>
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<td>2</td>
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<td><strong>Vascular disorders</strong></td>
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<td>Lymphangitis</td>
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<tr>
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<td>Unlikely</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Likely</td>
<td>17</td>
<td>13</td>
<td>50.00</td>
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</table>
A retrospective study on the efficacy and safety of intravenous immunoglobulin (Tegeline®) in patients with chronic inflammatory demyelinating polyneuropathy

which requires marked variations in neurological status before the score changes. The modified Rankin scale is less sensitive, however, and is easy to use in retrospective studies. Thus, the use of this scale in our study may have underestimated the responder rate. However, this possibility further demonstrates the robustness of the results: responders on the modified Rankin score are "true responder" patients with a clear improvement in their clinical status. The decision to use the responder rate at 4 months based on the investigators’ overall assessment as a secondary endpoint enabled us to take into account small variations in the patient’s status that were not detected using the modified Rankin scale and to study the progression over time because the evaluation was performed after each cycle of IV Ig between 0 and 4 months. Using the responder rate a 4 months also enabled us to assess transient improvements, considered as a response to treatment, which would have been accounted for by the INCAT ODSS, and improvements that did not lead to a change in the Rankin score. This approach explains the difference between the responder rate according to the modified Rankin score (52%) and according to the investigator (85.7%), with a better response to treatment according to the more subtle assessment by the investigator, although more subjective and determined after the fact, depending on the perception of the patient and on information recorded in the source medical files.

Overall, our responder rate to IV Ig (Tegeline®) at 4 months based on the modified Rankin score was significantly higher than the responder rate with placebo based on historical data in the literature (meta-analysis including results from the van Schaik and ICE studies), confirming a significant therapeutic effect of IV Ig.

Moreover, an analysis of the predictive factors of treatment response identified only one predictive factor: the mean dose of IV Ig administered per cycle with a minimum dose of 120 g per cycle. In our study, the median dose per cycle was 112.5 g. We could not draw conclusions based on this trend due to (among other reasons) the type of the study and the number of patients. It would be necessary to assess, in a clinical study, the impact of the doses administered per cycle on the efficacy of IV Ig irrespective of the patient’s weight. The number of cycles of IV Ig, which reflects the need to continue the cycles, was not found to be a predictive factor for treatment response; however, it is important to take into account the fact that the assessment concerned a relatively short period of time. The results of the randomized ICE study [20] on IV Ig versus placebo in which the cycles of IV Ig were administered every 3 weeks for at least 26 weeks suggest that continuing the cycles prevents relapses and leads to a long-term beneficial effect. In a literature review, Brannagan [35] also recommended the regular administration of IV Ig every 4 to 6 weeks rather than waiting for a relapse. Conversely, in a meta-analysis [28], van Schaik et al. were less supportive of systematic administration and recommended the observation of disease progression in the patient prior to deciding whether to re-administer treatment. Additionally, in our study, age, gender and time from the beginning of symptoms were not found to be predictive of response, which is consistent with the ICE study.

The efficacy results at 7 months were difficult to interpret because too many data were missing and too many patients were excluded, which introduced bias in the interpretation. The results nevertheless showed that responder patients at 4 months were still responders at 7 months.

Finally, the results of our study confirm the favorable safety profile of IV Ig in patients with CIDP, with adverse events that were only mild to moderate in severity, were resolved without sequelae and are classically described in the literature. The retrospective nature of the study, which most likely underestimates the incidence of more moderate AE's, is clearly an accuracy limitation.

References


