Randomised controlled trial comparing two different intravenous immunoglobulins in chronic inflammatory demyelinating polyradiculoneuropathy


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Randomised controlled trial comparing two different intravenous immunoglobulins in chronic inflammatory demyelinating polyradiculoneuropathy

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ABSTRACT

Background Different preparations of intravenous immunoglobulin (IVIg) are considered to have comparable clinical efficacy but this has never been formally investigated. Some patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) report that some IVIg brands are more effective than others. A liquid IVIg preparation is more user friendly and potentially can be infused at a faster rate.

Objectives The primary objective was to compare the efficacy of two different IVIg brands in CIDP. The secondary objective was to compare their safety.

Methods This was an investigator-initiated multi-centre randomised controlled double-blind trial. Twenty-seven patients with active but stable CIDP treated with their individual stable IVIg (Gammagard S/D) maintenance dose and interval were randomised to receive four infusions of freeze-dried 5% IVIg (Gammagard S/D) or the new liquid 10% IVIg (Kiovig). The overall disability sum score (ODSS) was used as the primary outcome scale. The equivalence margin was defined as a difference of ≤1 point in mean ΔODSS between treatment groups. Main secondary outcome scales were the MRC sum score and the Vigorimeter.

Results Repeated measurements analysis of variance, adjusted for baseline ODSS, showed a clinically insignificant treatment difference of 0.004 (95% CI −0.4 to 0.4). We also found no significant differences in any of the other outcome measures. Besides a lower occurrence of cold shivers in patients randomised to Kiovig (p=0.03), no significant differences were found in the occurrence of adverse events.

Conclusions This trial demonstrated equal clinical efficacy between a freeze-dried and a liquid IVIg preparation for maintenance treatment of CIDP.

INTRODUCTION

Clinical trials have proven the efficacy of intravenous immunoglobulin (IVIg) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).1−4 The efficacy of intermittent IVIg in CIDP has been shown to last for a period of at least 24 weeks.4 However, most patients need IVIg treatment for several years.5 In many CIDP patients, various brands of IVIg are used over the years, often depending on what is available in the hospital pharmacy.6 Although some authors recommend that switching between IVIg brands only occur under careful professional supervision, in practice this is usually done without any specific safety measures.7 IVIg is increasingly being used for various neurological conditions.7 Various IVIg brands are generally assumed to be equivalent,8−9 but some patients report some brands as more efficacious than others.7−10 When CIDP patients show no favourable response to IVIg it is not known whether treatment with an alternative brand might be beneficial. IVIg brands differ in their composition and production processes, which might affect their efficacy and tolerability.5−10−11 Whether this reflects differences in efficacy or safety in immune-mediated neuropathies has never been investigated and, therefore, trials comparing different preparations are recommended.12 The freeze-dried lyophilised brand Gammagard S/D has been used in randomised controlled trials in autoimmune polyneuropathies.13−14 The manufacturing process of the new liquid IVIg preparation Kiovig employs a Cohn-Onley cold alcohol fractionation procedure to isolate the IgG fraction, which is further purified using chromatography to yield a solution containing ≥98% IgG instead of ≥90% IgG in Gammagard S/D.15 Kiovig contains a different distribution of IgG subclasses and no added glucose, sodium or preservatives. It is more concentrated and can be infused at a faster rate with a reduced volume load.11

We compared the efficacy and safety of these two products in a controlled double-blind trial. A group of active but stable CIDP patients treated with a stable maintenance dosage of the 5% freeze-dried IVIg preparation were randomised to the same product or to an equivalent dosage of a more concentrated 10% liquid IVIg preparation.

METHODS

This investigator-initiated trial was conducted at three university-affiliated neuromuscular disease centres in the Netherlands and was approved by the Medical Ethical Committees of these centres and the competent authority. This study was conducted in compliance with the E6 International Conference on Harmonization guideline for Good Clinical Practice16 and following local regulations. Monitoring was conducted by an Association of Clinical Research Professionals (ACRP) accredited monitor. A data monitoring committee regularly assessed the progress of the trial and the safety data. Written informed consent was obtained from all patients. This CIC trial (comparing IVIg in
CIDP) is registered in the International Standard Randomised Controlled Trial number register as ISRCTN52121370.

**Subjects**

Inclusion criteria were:

1. Diagnosis of CIDP made by a consultant neurologist and fulfilling the American Academy of Neurology clinical research criteria.\(^1\)
2. Age \(\geq 18\) y.
3. Initial chronically progressive, stepwise progressive or recurrent weakness of all extremities, developing over at least 2 months, with reduced or absent tendon reflexes.
4. Observed and documented clear improvement of muscle function after the first use of Gammagard S/D.
5. Active CIDP defined by an overall disability sum score (ODSS)\(^2\) grade \(\geq 2\) and a Medical Research Council (MRC) grade \(\leq 4\) in at least one of the muscles assessed in the MRC sum score\(^3\) before start of the trial or following a reduction of IVIg dose at some time within the last 12 months before start of the trial.
6. Ongoing intermittent treatment with IVIg (Gammagard S/D) leading to a stable condition. The individual dose must have been stable (within a 25% range of the total dose) for at least 8 weeks and unchanged within the last 4 weeks before start of the trial.
7. Electromyography findings compatible with CIDP at least once during their illness.\(^6\)\(^7\)\(^8\)

Exclusion criteria were:

1. Known hereditary neuropathy or severe concomitant diseases such as HIV infection, Lyme disease, chronic active hepatitis, congestive heart failure, systemic lupus erythematosus, drug or toxin induced neuropathy, vasculitis and malignancies.
2. IgM paraprotein with anti-myelin-associated glycoprotein (MAG) antibodies.
3. Multifocal motor neuropathy (MMN), fulfilling the European Federation of Neurological Societies/Peripheral Nerve Society criteria.\(^9\)
4. Atypical CIDP with pure sensory or persistent unifocal impairment or significant central nervous system involvement.
5. Treatment with another IVIg brand than Gammagard S/D during the previous 8 weeks.
6. Participation in a controlled trial of a medicinal product within the last 12 weeks.

**Study design**

The trial consisted of 10 infusions in three phases. First, an open label phase with one Gammagard S/D infusion, second a double-blind phase with four blinded infusions and third an open-label phase with five Kiovig infusions (figure 1). Patients were treated in the hospital daycare centre or at home according to where they were treated prior to trial entry. Immediately before infusions 1 and 2 (baseline), 4 and 6 (blind phase), and 8 and 10 (open-label phase), a neurological examination, including the MRC sum score (6 muscles) and INCAT sensory sum score (ISS), was carried out by the assessor (KK). Before every infusion, the ODSS as well as the muscle grip strength (vigorimeter) were recorded (figure 1).\(^10\) During every infusion and 1 week thereafter the patient was asked to record adverse events (AEs). One week after each infusion the patient completed the following questionnaires: Fatigue severity scale (FSS\(^24\)), Short Form (36) Health Survey, Dutch language acute version 1 (SF-36\(^25\)) and the Rotterdam handicap scale (RHS\(^26\)).

**Study drug**

Patients were randomised to receive four infusions of 5% (50 g/l) freeze-dried IVIg (Gammagard S/D, Baxter AG, Vienna, Austria) or the new 10% (100 g/l) liquid IVIg (Kiovig, Baxter AG, Vienna, Austria). All included patients had been treated successfully with maintenance IVIg before start of the trial (mean 5 y; range 5 months to 13 y). For both brands, the IVIg dosage and frequency for each patient was kept the same as their treatment regimen prior to trial entry and remained constant throughout the whole trial. One central trial pharmacist was responsible for the reconstitution (if necessary), packaging, labelling and distribution of the trial medication during the double-blind phase.

**Randomisation and blinding**

We used a computer-generated randomisation list produced by a statistician (WH). A block randomisation was made for each centre. Patients were checked for eligibility and enrolled by the principal investigator (PD) in agreement with the main investigators of the three centres. The assessor allocated the next available number on entry after consent was given. Allocation concealment was ensured via sequentially numbered, opaque, sealed envelopes distributed by the statistician to the principal investigator. After randomisation, the prescription was faxed by the principal investigator to the pharmacy. Patients, the assessor (KK) and the blinded neurologist who assessed the AEs were all blind to the drug allocations. We did not dilute the 10% (Kiovig) solution to a 5% solution as we had no data regarding its stability. Due to the different volumes of the preparations, the nurses who were experienced in administering the IVIg could not be blinded for the drug assignment as they had to adjust the

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**Figure 1** Trial outline. ISS, INCAT sensory sum score; MRC, Medical Research Council; ODSS, overall disability sum score; RHS, Rotterdam handicap scale.
infusion speed to ensure the integrity of the blinding for patients. All patients were treated according to their individual established IVIg dosage prior to study entry. The infusion bag and the drip chamber were enclosed in a covering bag and a coloured infusion line was used so neither the assessor nor the patient was able to discern which brand was infused. The IVIg was infused at a standard safe infusion rate. To check whether blinding was maintained, both patients and the assessor were asked after the blind phase and at the end of the trial to guess which drug they thought had been administered in the blind phase.

Allocation was revealed after all patients had completed the study and data entry had been declared complete.

**Efficacy**

The primary objective was to study the efficacy of Kiovig compared to Gammagard S/D in the treatment of CIDP; the ODSS was used as the primary outcome measure. Before the trial started, we predefined in the protocol that a difference in the mean ODSS change from baseline between the two groups of ≥1 point was considered as equivalence. The two ODSS measurements, assessed immediately before infusion one (Gammagard) and two (first blinded infusion), were averaged and the mean value was taken as a baseline measurement. Changes in the vigorimeter values and the MRC sum score were used as secondary outcome measures as were all other measures.

**Safety**

The secondary objective was to compare the safety of both products. A questionnaire regarding AEs was completed by the patients during every infusion and again 1 week later. A neurologist blinded to the allocation of trial medication (EB, EC, AK) evaluated AEs by telephone at regular intervals.

**Statistical analysis**

The sample size calculation based on historical data showed a SD of 0.84 for ΔODSS (over a stable period of 2 months). To exclude differences of ≥1 point in ODSS, 11 patients were required in each treatment group (α=0.05, power 80%). The mean of ODSS changes from baseline for each of the four blinded infusions (infusions 3, 4, 5, 6) was compared using repeated measurements analysis of variance (ANCOVA). As an operational criterion for equivalence, the 95% CI for the difference in the mean ODSS should not cross the values −1 and +1.

For all other outcome measures, the change from baseline was calculated by taking the mean of the scores during the double-blind phase and comparison was done with analysis of covariance (ANCOVA) with baseline value as covariate. Data were analysed according to the intention-to-treat principle.

All AEs were recorded. The statistical analysis for the objectives of the study was based upon data from the double-blind phase. The open-label Kiovig phase was primarily used to gain more safety information. The occurrences of AEs were compared using χ² or Fisher exact test. Analysis was performed using SPSS V.15.0 and SAS V8.1.

**RESULTS**

From December 2007 to September 2008, 75 CIDP patients were screened for eligibility; 48 were excluded mainly because they were not treated with IVIg on a regular basis or had no signs of active disease (figure 2). Other reasons for non-eligibility were treatment in a different hospital than the neuromuscular centre where the diagnosis was established or treatment with another brand of IVIg (two patients). In total, 27 patients were randomly assigned for eligibility (n=75). Excluded (n=48). Not meeting inclusion criteria (n=39). Refused to participate (n=2). Other reasons (n=7). All but one patient received the total amount of four blinded infusions. This patient decided to stop the blind treatment after one infusion due to an AE (fatigue). This patient was observed while being treated unblinded with Gammagard S/D during the rest of the double-blind phase and included in the analysis according to the intention-to-treat principle. Two patients had a deterioration 8 months before the start of the trial. Another patient had a documented deterioration 11 months before entry and one patient had end-of-dose complaints before and during the trial.

All but one patient received the total amount of four blinded infusions. This patient decided to stop the blind treatment after one infusion due to an AE (fatigue). This patient was observed while being treated unblinded with Gammagard S/D during the rest of the double-blind phase and included in the analysis according to the intention-to-treat principle. One patient decided not to continue with the open-label phase regardless of what was given in the double-blind phase. Baseline and demographic characteristics were similar in the two groups (table 1).

**Treatment efficacy**

The treatments were not significantly different in efficacy in the primary outcome measure (difference 0.004 (Gammagard minus Kiovig), 95% CI −0.4 to 0.4), using repeated measurements ANOVA, and this effect did not differ significantly between the four measurements in the blinded phase (p=0.19). The ODSS showed a similar distribution between both groups (figure 3). Using ANCOVA, there were no clinically relevant differences between the two treatments in all outcome measures (table 2). In the patient who received trial medication only once during the blinded phase, the ODSS score after this treatment was exactly the same as after the non-trial medication. One patient required another IVIg dosage in the open-label phase due to a minor deterioration.
been successful. In 25 cases (93%) the assessor had no idea about
administered during the blind phase to check if blinding had
Blinding
Both IVIg brands were well tolerated. There were no signi
Treatment tolerance
Both IVIg brands were well tolerated. There were no significant
differences between the two treatments in the number of commonly reported AEs except for the lower occurrence of cold shivers in patients randomised to Kiovig (table 3). Altogether, 4 out of 14 patients in the Kiovig treatment group versus 1 out of 13 patients in the Gammagard S/D group (p=0.53) reported their AEs to be ‘severe’ in the questionnaires. The number of patients who reported AEs to the blinded neurologist was similar in the two groups (8/14 in the Kiovig vs 7/13 in the

DISCUSSION
In this study we compared the efficacy of a freeze-dried IVIg (Gammagard S/D) with a liquid preparation (Kiovig) for the treatment of CIDP. We found no significant difference in clinical efficacy as the 95% CI for the difference of mean ODSS was within the interval −1 to +1. Equivalence in this study was primarily based on the ability to carry out everyday functions measured using a disability scale (ODSS) validated in Guillain-Barré Syndrome (GBS) and CIDP. No significant differences were found between the two preparations for all other outcome measures, including impairment scales regarding muscle strength and sensory symptoms, and scales measuring handicap, fatigue and quality of life.

**Table 1** Baseline demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Gammagard S/D (n = 13)</th>
<th>Kiovig (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>54.0 (12.0)</td>
<td>54.6 (13.8)</td>
</tr>
<tr>
<td>Men</td>
<td>8 (62%)</td>
<td>12 (88%)</td>
</tr>
<tr>
<td>IVIg dosage (g/week)</td>
<td>12.5 (8–30)</td>
<td>14.6 (10–38)</td>
</tr>
<tr>
<td>IVIg interval (days)</td>
<td>18.8 (5.3)</td>
<td>15.5 (4.1)</td>
</tr>
<tr>
<td>Bodyweight (kg)</td>
<td>78.5 (13.2)</td>
<td>85.6 (12.5)</td>
</tr>
<tr>
<td>ODSS score* (range 0–12)</td>
<td>3.0 (0–7)</td>
<td>3.7 (1–5)</td>
</tr>
<tr>
<td>MRC sum score* (range 0–60)</td>
<td>53.6 (4.4)</td>
<td>54.6 (3.4)</td>
</tr>
<tr>
<td>Vigorimeter* (range 0–160 kpa)</td>
<td>89.3 (46.2)</td>
<td>86.8 (31.0)</td>
</tr>
</tbody>
</table>

Data are number (%), mean (SD) or median (range). Higher overall disability sum score (ODSS) values indicate more limitations. Higher Medical Research Council (MRC) sum score values and vigorimeter scores indicate greater strength.

*Mean value of the two measurements before randomisation at baseline.

**Table 2** Primary and secondary efficacy outcomes

<table>
<thead>
<tr>
<th></th>
<th>Difference (Gammagard minus Kiovig)</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>ODSS</td>
<td>−0.04 to 0.4</td>
<td>0.98</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td>MRC sum score</td>
<td>−1.9 to 0.7</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>Vigorimeter</td>
<td>−4.0 to 5.0</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>ISS</td>
<td>−0.7 to 1.8</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>FSS</td>
<td>−1.9 to 0.6</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>RHS</td>
<td>−0.2 to 1.6</td>
<td>0.12</td>
</tr>
<tr>
<td>SF-36</td>
<td>Physical functioning</td>
<td>−4.5 to 0.28</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Role-physical</td>
<td>−3.6 to 7.2</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>Bodily pain</td>
<td>−6.6 to 6.1</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>General health</td>
<td>−4.8 to 1.0</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td>Mental component summary</td>
<td>−2.4 to 5.4</td>
<td>0.43</td>
</tr>
</tbody>
</table>

Data shown are differences from analysis of covariance with adjustment for baseline values with 95% CI and p value.

**Table 3** Number of patients who reported common adverse events during the blind phase

<table>
<thead>
<tr>
<th>Adverse events (blinded phase)</th>
<th>Gammagard S/D (n = 13)</th>
<th>Kiovig (n = 14)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>10 (77%)</td>
<td>10 (71%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Muscle and joint ache</td>
<td>8 (62%)</td>
<td>9 (64%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (62%)</td>
<td>6 (43%)</td>
<td>0.33</td>
</tr>
<tr>
<td>Itching</td>
<td>5 (38%)</td>
<td>6 (43%)</td>
<td>0.82</td>
</tr>
<tr>
<td>Backache</td>
<td>3 (23%)</td>
<td>6 (43%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (38%)</td>
<td>4 (29%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Warm feeling</td>
<td>3 (23%)</td>
<td>5 (36%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Skin rash</td>
<td>3 (23%)</td>
<td>5 (36%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Pain at infusion area</td>
<td>3 (23%)</td>
<td>4 (29%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Cold shivers</td>
<td>6 (46%)</td>
<td>1 (7%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Data are number (%) and compared using χ² test or Fisher exact test.

**Figure 3** Scatterplot overall disability sum score.
An in vitro model of immune neuropathy found a comparable efficacy of eight different IVIg products. A different response to various IVIg brands has been described in a randomised trial in primary immune deficiency. In Kawasaki disease, retrospective studies reported similar as well as different responses to various brands. An open study reported no clinical differences between Gammagard and Kiovig in MMN. As far as we know, no RCT has been published that evaluated differences between IVIg brands in neurological disorders.

The two preparations had similar AEs and there were no problems with the transition from one preparation to the other. Cold shivers were less common in patients treated with the liquid brand, which might be caused by less aggregates and excipients in Kiovig. Ascept meningitis or neutropenia as AEs after IVIg are reported to be unrelated to the proprietary formulation. A group of 50 healthy subjects showed no difference in tolerance to two different IVIg preparations including one liquid form. A retrospective study in Kawasaki disease reported more infusion-related rigors in one IVIg brand than in another.

Since one IVIg preparation was more concentrated (10%), it was not possible to blind the nurses who administered the trial drug because the IVIg dosage as well as the duration of administering had to be equal for both preparations. Therefore, the nurses were trained thoroughly in maintaining the blind. By asking the patients to report which drug they thought they had received we could show that blinding had been successful. Randomisation was successful as clinical characteristics were well-balanced between the treatment groups.

To ensure that the CIDP patients were still IVIg dependent they had to have had at least moderate disability in arms or legs at baseline or following IVIg reduction during the previous 12 months. Most patients additionally had had at least some documented worsening of their CIDP within the 5–6 months before start of the study and some also had minor fluctuations in their clinical course after they had completed the trial. To make sure no IVIg refractory patients were included, only patients who initially improved after IVIg, being in a stable condition using a stable maintenance dose of IVIg and who were considered to need IVIg treatment were included.

Previous international trials regarding the efficacy of IVIg in CIDP used treatment periods of ≤6 weeks. Therefore, the double-blind treatment period of four infusions, administered over a time period of 6–16 weeks (mean 10 weeks) due to the different inter-individual intervals, seems reasonable as the half-life time of IVIg is about 5 weeks. Since we only compared two different IVIg brands manufactured by the same pharmaceutical company with each other, we can only draw conclusions about the equivalence of these two products. Logistically, it was not feasible to compare more available brands. However, our results suggest that the clinical effects of a new liquid IVIg product are similar to a non-liquid product that has been used for several decades.

In specific situations certain brands are recommended, such as IVIg preparations that contain less IgA in patients with a low IgA level and preparations containing less sucrose in patients with kidney disease. Liquid IVIg preparations do not need reconstitution prior to use and can potentially reduce the infusion time, but this was not investigated in this study.

Although some patients may prefer certain IVIg brands, this trial suggests that this is unlikely to be caused by differences in clinical efficacy or tolerance between a freeze-dried and a liquid product. As we showed no significant clinical differences between these two IVIg brands in their efficacy to treat CIDP it seems reasonable to assume that this will also apply for other diseases treated with IVIg.

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**Funding** This study was supported by an unconditional grant from Baxter Healthcare BV, The Netherlands.

**Competing interests** K Kuitwaard was assigned to conduct a study comparing Gammagard S/D with Kiovig (this study) supported by an unrestricted departmental research grant from Baxter. L H van den Berg received fees for lecturing and consultancy from Baxter BV. W-L van der Pol received personal compensation from Baxter International for serving on a scientific advisory board. R van Schalk received an unrestricted departmental research grant from Sanquin Blood Supply Foundation and from Actelion Pharmaceuticals Ltd; personal and departmental payments for lecturing and consultancy from Actelion Pharmaceuticals Ltd; received government research support NOW grant #940-33-024 and NOW grant #093-51-201 unrelated to subject of publication; received support from the non-profit foundation Princes Beatrice Fonds grant #MAR01-2013 and serves as a member of the Cochrane Neuromuscular Disease Group editorial board. PA van Doorn received an unrestricted departmental research grant from Baxter to conduct a study comparing Gammagard S/D with Kiovig (this study) and to conduct a previous study comparing Gammagard S/D with or without methylpredisolone in GBS; received personal and departmental payments for consultancy/RCT trial boards from Talecris, ZLB, Baxter and Octapharma; received government research support from ZonMW; received support from the non-profit foundations Princes Beatrice Fonds and Janvio Foundation unrelated to this study and serves as a member of the Cochrane Neuromuscular Disease Group editorial board.

**Ethics approval** This study was conducted with the approval of the Erasmus MC, University Medical Center, Rotterdam, The Netherlands; University Medical Center Utrecht, Utrecht, The Netherlands; Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

**Contributors** All authors have contributed in the conception and design of the trial, acquisition of data or analysis and interpretation of data, drafting of the article or revising it critically for important intellectual content. All authors gave final approval of the version published/submitted.

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