Cost-utility analysis of intravenous immunoglobulin and prednisolone for chronic inflammatory demyelinating polyradiculoneuropathy

Cost-Effectiveness Analysis of Intravenous Immunoglobulin and Prednisolone for Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

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September 2001

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Abstract

There is a paucity of economic evidence relating to interventions for peripheral nerve disorders and the aim of this study was to illustrate the application of economic evaluation in this area by making a comparison of the cost-effectiveness of intravenous immunoglobulin and prednisolone treatment for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Patients (n=32) were recruited to a double-blind randomised cross-over trial from nine European centres and received either prednisolone or intravenous immunoglobulin during the first six-week treatment period, followed by a four-week washout period after which the other treatment was received. Service use, quality of life and physical disability were measured at baseline and at the end of both treatment periods. Cost and outcome data were available for 25 patients who completed the first arm of the study but for only 16 who completed both arms. Therefore, the focus of the economic evaluation was on the initial treatment period. Baseline costs were controlled for using a bootstrapped multiple regression model. The cost difference between the two treatments was estimated to be £1608 for the initial six week period. Physical disability fell over six weeks in both groups without any significant difference between them. Health-related quality of life, as measured by the EQ-5D, increased more in the IVIg group and this difference approached statistical significance. The incremental cost per QALY of IVIg compared to prednisolone was estimated to be £107,200. The cost per QALY is greatly affected by the price of IVIg and the amount administered. The impact of side effects on long-term costs and quality of life are likely to reduce the cost per QALY of IVIg treatment compared to prednisolone.

Key words

chronic inflammatory demyelinating polyradiculoneuropathy

intravenous immunoglobulin

prednisolone

health care costs

quality-adjusted life years

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a peripheral nerve disorder which is estimated to effect between one and two people per 100,000 population [1,2]. It is characterised by slow onset of weakness and reduced sensation. It is a prolonged illness that has been shown to respond to a number of treatment regimes including intravenous immunoglobulin (IVIg), corticosteroids and plasma exchange [3-8]. Each of these interventions appears to be efficacious in the short term but little is known about the long-term effects. There are specific concerns with all three treatments, in particular with regard to the known adverse effects associated with long-term use of corticosteroids and the perceived high cost of IVIg and plasma exchange.

Since health care resources are finite, it is important to consider the economic implications or cost-effectiveness of different health care interventions. This does not mean that interventions that have a relatively low cost are to be preferred to those that are expensive; rather we should examine the outcomes that can be achieved from spending money in one way compared to another. Higher cost treatments may produce better outcomes and therefore prove to be cost-effective. In addition, a treatment that appears to be expensive may result in reduced costs elsewhere in the health care system (currently or in the future). Conventionally, cost-effectiveness analysis combines information on the cost of treatment with information on outcomes measured in *disease-specific* units. However, decision makers may want to compare interventions in one area of medicine with those in another and this has led to a particular form of cost-effectiveness analysis called cost-utility analysis which measures outcomes in *generic* units, typically quality-adjusted life years (QALYs).

Economic evaluations are rare in the area of peripheral nerve disorders, but there have been studies of the use of plasma exchange for Guillain-Barré Syndrome [9, 10] and one comparing IVIg and plasma exchange for the same condition [11]. However, no previous cost-effectiveness analyses of treatments for CIDP appear to have been conducted. We recently reported a randomised controlled trial comparing IVIg and oral prednisolone in CIDP [12]. The aim of this part of the study was to compare the cost-

effectiveness of these treatments in terms of the relative costs of reduced physical disability and costs per QALY gained.

Methods

Sample and interventions

Details of the clinical trial methodology have been reported elsewhere [12]. In brief, the study was designed as a double-blind crossover randomised controlled trial. Patients were drawn from nine European centres and, after giving informed consent, were randomly allocated to initially receive either oral corticosteroids (prednisolone) or IVIg (as well as placebos of the other treatments). The inclusion criteria were: (i) clinical diagnosis of CIDP, (ii) progressive or relapsing motor and sensory dysfunction of more than one limb over more than two months caused by neuropathy, (iii) reduced or absent tendon reflexes, (iv) less than ten white cells/µl in the cerebrospinal fluid, (v) fulfilment of neurophysiological criteria (prepared by the research group) for multifocal demyelinating polyradiculoneuropathy, (vi) significant physical disability in upper or lower limb function, and (vii) stable or worsening clinical condition. Patients were excluded if they (i) had associated systematic diseases that could be associated with neuropathy, (ii) were or planned to be pregnant, (iii) had concurrent medical conditions which could effect treatment, (iv) had significant respiratory impairment, (v) had received IVIg, corticosteroids or plasma-exchange in the six weeks before treatment, (vi) were under the age of 18, (vii) met the criteria for multifocal motor neuropathy and (viii) had previously failed to respond to IVIg or corticosteroids.

The initial treatment period lasted six weeks, followed by a four-week washout period, after which the second six-week treatment period with the other intervention commenced. The regimen for prednisolone was 60 mg per day during the first two weeks, 40 mg per day in week three, 30 mg per day in week four, 20 mg per day in week five and 10mg per day in week six. Administration of IVIg involved a hospital stay (assumed to be one night on a neurological ward) and consisted of 2 g Sandoglobulin (Novartis) per kg of body weight (a standard weight of 75 kg was used for the analyses).

Service use and costs

Our objective was to measure service use to ascertain the overall impact of the interventions on health care costs. The Client Service Receipt Inventory (CSRI) [13], previously used in areas such as mental health care, was adapted specifically for the study and administered four times (covering the six month period prior to baseline, the first treatment period, the washout period and the second treatment period). The CSRI provided details of accommodation, employment, income, service receipt and informal care provided by friends and family. The service receipt and informal care sections provided the most relevant information for the calculation of service costs. Information was collected on stays in hospital (intensive care, acute and rehabilitation wards), outpatient visits (neurology and other) and attendances at day hospitals. Details of the number and average length of contacts with the following community services were also collected: physiotherapists, occupational therapists, general practitioners, nurses, social workers, surgical appliance officers and chiropodists. Patients could also specify other services which they had received. Finally, the number of hours per week spent by family and friends in specific caring activities was identified.

Unit costs were then attached to the measures of service use. Ideally unit costs would be calculated for each specific site but given the relatively small sample size this was considered to be impractical. Where country specific costs were not known, and so that costs could be expressed in a common currency, unit costs of services in the UK were either divided by appropriate medical cost indices [14] or, if these were not available, by the ratio between the *purchasing power parity index* (produced by the OECD and which takes account of differences in the cost of living between countries) and the exchange rate. The unit costs used in the study are shown in Table 1. The figures for intensive care, rehabilitation and acute wards were taken from a resource costing study within a multi-national neurological trial by Schulman et al [14] whilst other unit costs were from a recognised UK source [15]. Informal carers do not receive remuneration but their activities still potentially have an economic value and the unit cost of a home care worker was used as a proxy for this service.

At the time of the study (1997-98), the cost per gram of IVIg in the UK was approximately £13. The cost per day on a neurological ward in the UK was estimated to

be £208 [15]. The cost of prednisolone was estimated to be £5 for the six week treatment period. The costs of the drugs themselves were *not* adjusted according to the ratio between the purchasing power parity index and the exchange rate on the grounds that drug prices are subject to a different set of cost drivers compared to hospital services, etc. The impact that different IVIg prices had on the results was explored using sensitivity analyses.

Service use and costs associated with IVIg and prednisolone were initially compared for all patients who completed both treatment periods. Comparisons of the proportion of patients using specific services were made and tests of significance were performed using McNemar's test for paired dichotomous variables. Differences in costs for the two treatments were tested for significance using paired and independent sample t-tests and non-parametric tests, and tests were also conducted for the presence of period and carry-over effects [16]. Since a relatively large number of patients did not complete both arms of the trial, the main analysis was conducted for those completing the first treatment period, using a multiple regression model to adjust for baseline costs.

Cost data are often skewed and this can result in non-normally distributed residuals. In order to adjust for this potential problem we used a non-parametric bootstrapping technique which does not rest on this assumption of normality [17]. This procedure involved resampling with replacement from the original data set. If a large enough number of samples are drawn from the original then it is assumed that the population distribution of the parameter of interest is approximated. Here, two thousand samples were drawn and a bias-corrected 95% confidence interval based on these samples was produced.

Cost-effectiveness analysis

Details of the choice of clinical outcome measures used in the trial are given by Hughes et al [12]. The primary outcome measure was the change in physical disability level after two weeks. However, service use and costs are more appropriately measured over a longer time frame and in this study a six-week period was used. Therefore, the relevant measure of effectiveness here is the change in physical disability level over six weeks. The disability scale measured arm and leg disability, and for each it ranged

between zero (no upper limb problems/walking not affected) to five (unable to use either arm for any purposeful movement/restricted to wheelchair, unable to stand and walk a few steps with help). The sum of the scores was used in the analyses and the focus was on the change in this during the first treatment period.

Because improved patient outcomes may be achieved at a relatively high cost we were interested in the *incremental cost-effectiveness* of one treatment compared to the other (IVIg compared to prednisolone), i.e. how much extra (or less) does it cost to gain one extra unit of improvement by using IVIg rather than prednisolone? Consequently the incremental cost effectiveness ratio is defined as the ratio between net costs (the mean cost of IVIg treatment minus the mean cost of prednisolone treatment) and the net benefits (the mean reduction in physical disability resulting from IVIg treatment minus the mean reduction in physical disability resulting from prednisolone).

Cost-utility analysis

In order to assess the broader impact of the two interventions and to generate results that could be compared with those produced from studies of health care interventions in different areas, we recorded changes in health-related quality of life using the EuroQol EQ-5D instrument [18]. This instrument permits preference-weighted measures of health-related quality of life to be generated. The EQ-5D consists of five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) each of which has three levels of severity (1 - no problem, 2 - some problem and 3 - serious problem). Different combinations of these scores were converted into a utility index score (with one representing full health and zero representing death), based on a community-based survey of preferences for different health states coded in this way [19]. In addition to the use of community values for valuing different health care states, the EQ-5D also includes a visual analogue scale, running from 0 to 100, on which the patient marks a position which indicates their quality of life on that day. This allows a patient self-rated measure of utility to be obtained.

QALYs provide a way of combining the length of time in a particular health state with the quality of that time. For example, if an individual has an illness such as CIDP which results in a reduced level of quality of life to, say, 0.6 for one year then one year lived

with this condition would represent 0.6 QALYs. To calculate the number of QALYs gained by the interventions in question, the change in quality of life over the first treatment period was calculated for each patient and multiplied by 6/52 (since the treatment period only lasted for six weeks). As before, the incremental cost per QALY ratio was calculated by dividing the net costs of IVIg by the net difference in QALYs.

Sensitivity analyses

Cost-effectiveness analysis involves a level of uncertainty concerning estimated costs and outcomes and it is important to test the robustness of baseline findings by altering key parameters. To do this we first examined the range of cost-effectiveness findings by using the upper and lower limits of the 95% confidence intervals around the mean difference in costs and outcomes between the two groups. Second, because one of the main issues surrounding the use of IVIg is its price we examined the effect of using alternative figures (personal communication from Genesis Medical Marketing Consultants) which represented: (i) the range of prices for different immunoglobulin brands current (2001) in the UK (£12.20 to £18; personal communication from the pharmacy department of Guy's Hospital), (ii) the current price per gram in the United States (£63 per gram; personal communication from Genesis Medical Marketing Consultants) and (iii) the lowest price reported during the past ten years (£7 per gram; personal communication from Genesis Medical Marketing Consultants).

Short- and long-term cost effectiveness

The main outcome measure used in the trial was the change in physical disability two weeks after the start of each treatment. Since we cannot confidently estimate service costs for this two-week period – costs during the longer six-week period of measurement are likely to have been spread unevenly – we restrict our analysis of short-term cost-effectiveness to the difference between drug costs alone. Figures need to be treated with caution accordingly.

To ascertain fully the relative cost-effectiveness of prednisolone and IVIg treatment for CIDP we need to consider the long term situation. CIDP is a chronic condition and in many cases repeated treatment is required. However, evidence is lacking in a number of crucial areas, in particular: (i) the dose of IVIg and prednisolone required in the long-

term, (ii) the frequency with which IVIg needs to be administered, (iii) the proportion of patients who improve sufficiently so as to not require further treatment, and (iv) the probability of side effects caused by the two treatment regimes. Therefore, any long-term indications of relative cost-effectiveness must at present be speculative.

In order to examine the potential long-term effects we present three different treatment scenarios differentiated according to the amount of IVIg that is administered. The typical dose is 2g/kg every six weeks [5] but Hahn et al [6] report that the amount of IVIg required as a maintenance therapy may be lower than 1g/kg for some patients. We therefore considered the potential effect of reducing the average amount to 1g/kg and 1.5g/kg after the initial six week treatment period, and we compared these with a situation where 2g/kg continued to be administered every six weeks. We did not vary the amount of prednisolone as this has such a low unit cost that any effects would be insubstantial. We assumed that for each treatment scenario the difference in quality of life and physical disability as observed during the six week period would be maintained over the period of one year. We also assumed that, after the initial treatment period, the use of other services would not differ between patients receiving prednisolone and those receiving IVIg. Annual costs based on these three treatment scenarios were calculated and differences between the two treatments were estimated, again after controlling for baseline costs using bootstrapped regression analysis.

Finally we considered the long-term impact of side effects on the results. Evidence is lacking on the prolonged use of IVIg and prednisolone for patients with CIDP. However, we were able to gain speculative insight of the cost impact of the latter by referring to a study of the use of steroid treatment for patients who had undergone renal transplantation. This group has some similarities in that prolonged use of high dose steroids is common.

Results

Sample description

Thirty two patients were entered into the trial. Service use, costs, six-week physical disability scores and quality of life scores were available for 25 (78%) patients for the

first treatment period of the study. For 16 patients (50%) these measures were also available for the second period. Of the nine patients for whom data were available for the first period but not the second, three (two receiving IVIg during the first period, one prednisolone) required further treatment prior to the end of the washout period, two (one IVIg, one prednisolone) were not severe enough to require further treatment, one (IVIg) withdrew during the second period, one (IVIg) did not start the second period and for two (both IVIg) service use data were not collected for the second period. Therefore, of these nine patients seven had initially received IVIg and two prednisolone.

The baseline characteristics for the sample are given in Table 2. Overall there were few substantive differences between patients in the two treatment arms. For the sample with complete data relating to the first treatment period the main difference between the two groups was for worst leg disability grade in any attack where the score was higher for the IVIg group (p=0.065). No other differences approached statistical significance for these patients or those included during both treatment periods.

Service use and costs

Details of the service use and costs for the baseline and initial treatment periods are given in Table 3. The baseline figures reveal substantial use of out-patient and community based services. During the treatment period the prednisolone group's costs were dominated by in-patient care (88% of the total) whilst for the IVIg group the immunoglobulin made up most of the cost (94%). Total mean costs in the IVIg group were £799 higher than for the prednisolone group (t-test, p=0.499). However, the median costs were very different (£5 vs £2204) and the Mann-Whitney test revealed that the distributions were also significantly different (p=0.003).

Randomisation should have ensured that baseline differences were not biased. However, two patients with substantial in-patient costs during the six-month baseline period were both randomised to receive prednisolone during the first treatment period *before* these in-patient stays had ended and discharge only occurred *during* the initial treatment period. In a small sample this could result in biased costs with those for the prednisolone group being artificially high. One solution to this 'failure' of randomisation would be to remove the in-patient costs. However, this ignores the fact

that in-patient episodes may occur because of CIDP and may be shortened by effective treatment. Therefore, it was considered necessary to include in-patient costs but to control for baseline costs. A multiple regression model was used with the cost from the first treatment period as the dependent variable and baseline costs and treatment group used as independent variables. This revealed that IVIg costs were £1609 (95% confidence interval, £921 to £2296) greater than those for prednisolone and this difference was highly significant (p=0.014). Baseline costs also had a significant impact on treatment costs (coefficient=1.21, p<0.001). Overall the model could explain 93% of variation in treatment costs. The distribution of the regression residuals was slightly skewed and the bias–corrected 95% confidence interval of the cost difference, produced by bootstrapping, was £700 to £2185.

Cost-effectiveness and cost-utility

There was a statistically significant reduction in mean overall physical disability between the baseline and the sixth week from 3.5 to 2.7 for the prednisolone group (paired sample t-test, p=0.035) and a smaller reduction from 3.3 to 3.0 for the IVIg group (p=0.489). The prednisolone group therefore had a mean reduction in physical disability that was 0.5 higher than the IVIg group (95% confidence interval, -0.69 to 1.71). Over the treatment period prednisolone was therefore dominant (better outcome at a lower cost).

Over the same period, quality of life, measured by the EQ-5D, was largely unchanged (0.64 to 0.63) for the prednisolone group (p=0.956), whilst there was a relatively large improvement in quality of life (from 0.57 to 0.69) for the IVIg group (p=0.072). IVIg resulted in a mean relative gain in quality of life of 0.13 and this was close to being statistically significant at the p<0.05 level (95% confidence interval, -0.05 to 0.30) compared to prednisolone over the six week period. Multiplying 0.13 by 6/52 gives the number of QALYs gained through IVIg compared to prednisolone, i.e. 0.015. The incremental cost-utility ratio (£1609/0.015) shows that for IVIg to produce one more QALY than prednisolone a cost of £107,267 would be incurred.

Quality of life measured by the self-rating scale component of the EQ-5D fell from 56.3 to 53.7 in the prednisolone group (paired sample t-test, p=0.600) and increased from

48.3 to 58.5 in the IVIg group (p=0.101). There was a net gain in quality of life for IVIg compared to prednisolone of 12.8 (95% confidence interval, -2.8 to 28.5), or 0.13 on a 0-1 scale (the same change score as that derived using community values).

Sensitivity analyses

The incremental cost-effectiveness ratios (showing the extra cost of achieving a reduction in physical disability or an increase in QALYs gained by using IVIg) that were calculated using the upper and lower bounds of the 95% confidence intervals around the mean cost and mean changes in outcome are shown in Table 4. Using the physical disability outcome measure, IVIg is both less effective and more costly than prednisolone in producing a one-point improvement under the lower-bound and baseline estimates, but if the higher 95% CI disability score is assumed IVIg becomes more effective. The results for the community- and patient-rated changes in utility are similar and both show that if the lower bound EQ-5D values are taken, prednisolone is dominant but if the higher bound values are considered, the cost per QALY gained by IVIg drops to less than a half of the baseline estimates. Even greater reductions (to around £20,000 per QALY) are possible if the lower bound of the cost difference and the upper bound of the quality of life difference are used.

If a low current UK price is used (£12.20 per gram) then the average cost difference between the two treatments is £1489 (bias-corrected 95% confidence interval, £580 to £2065) and with a high current UK price (£18 per gram) the difference is £2359 (bias corrected 95% confidence interval, £1460 to £2933). If a price reported for the United States (£63 per gram) were used the difference would be £9109 (bias corrected 95% confidence interval, £8167 to £9677). Finally, if the price were at the lowest level during the past ten years (£7) then the cost difference becomes £709 (bias corrected 95% confidence interval, -£144 to £1297) which is not statistically significant.

Combining the findings for the current range of mean cost differences in the UK (i.e. with a price between £12.20 and £18 per gram) with the mean changes in outcome suggests that the current cost of achieving one extra QALY by using IVIg is between £99,267 and £157,267. If prices fell to £7 per gram the incremental cost per QALY

would be £47,267, whilst the worst case scenario for IVIg (a price of £63 per gram) implies an incremental cost per QALY of £607,267.

Short- and long-term considerations

The focus here has been on the costs and outcomes over a six week period of treatment, during which time physical disability fell more in the group treated with prednisolone. However, Hughes et al. [12] report that two weeks after treatment started the physical disability score fell by 1.24 in the group treated first with IVIg and by 0.53 in those treated first with prednisolone. Using the cost of medicines only for these 32 patients, i.e. an average cost of £2147 for IVIg, and £3 for prednisolone, the incremental cost-effectiveness ratio for IVIg (the difference in drug costs divided by the difference in outcome) amounts to £3020 and the cost per 0.5 units improvement – considered by Hughes et al. [12] to be clinically significant – is half this (£1510).

If prednisolone continues to be taken at a dosage of 10 mg per day and if 2 g/kg of IVIg are administered every six weeks then the annual cost difference is estimated to be £18,628 (bias-corrected 95% confidence interval, £17,098 to £18,700). However, if the amount of IVIg received after the initial six week period is 1g/kg then the difference is £10,624 (bias-corrected 95% confidence interval, £9633 to £11,202). Finally, if after the initial six week period 1.5g/kg of IVIg is administered every six weeks then the difference in costs becomes £14,363 (bias-corrected 95% confidence interval, £13,341 to £14,959). Assuming that the mean difference in quality of life (0.13) is maintained throughout the year, these three scenarios produce incremental costs per QALY for IVIg compared with prednisolone of £139,246, £81,723 and £110,485 respectively. It should be re-emphasised that after the six week initial period only drug costs are included in these figures

Impact of side effects

Veenstra et al [26] report findings which suggest that in renal transplant patients who typically receive high doses of steroids over prolonged periods of time the incidence of hypertension is 15%, diabetes mellitus 10%, peripheral fractures 2%, avascular necrosis of the hip 8% and cataracts 22%. The mean annual health care costs of these side effects was estimated to be $530 in 1996 prices (approximately £350 in 1998 prices). If such

effects were experienced by CIDP patients using steroids, and if non-healthcare costs were included, and because of side effects quality of life was reduced, then other things being equal the incremental cost per QALY of IVIg would be reduced. The base case cost difference for one year is £18,102, but if prednisolone results in side effect costs of £350 then the difference would be £17,752. If, because of these side effects, the quality of life difference was 0.2 rather than 0.13, then the incremental cost per QALY associated with IVIg would be £88,760. If the annual cost of steroid related side effects were increased to £1000 then the incremental cost per QALY for IVIg would be £85,510.

Discussion

This study was designed as a crossover trial. However, a high proportion of the sample only completed the first arm of the trial and these were more likely to have dropped-out after receiving IVIg. If drop-outs occurred due to improvement following IVIg treatment then inclusion of only those receiving both treatments would bias the outcomes in favour of prednisolone. Therefore, it was decided to focus on the first treatment period. It was further discovered that randomisation had not been effective with regard to baseline service use and costs as two patients in the initial prednisolone group had been high users of in-patient care during the baseline period and these episodes continued into the treatment period thus artificially inflating the prednisolone costs. Regression analysis was used to control for baseline costs and the estimated mean cost difference for the six week period was £1608. This cost difference, when coupled with the better quality of life outcome associated with IVIg, revealed that it would cost £107,267 for IVIg to produce one extra QALY compared to prednisolone. The sensitivity analyses revealed that there was potentially substantial variation around these costs, primarily as a result of changing the price of IVIg. Incremental costs per QALY of around £20,000 were shown to be consistent with the 95% confidence intervals of the cost and quality of life differences as were situations where prednisolone was dominant..

Although we measured comprehensive service costs, the costs and cost-effectiveness of IVIg treatment were almost totally determined by the price of the IVIg itself. Other

services contributed relatively little to total cost. Clinicians may have little or no control over the price of IVIg but they do have influence over the frequency with which it is administered and the amount that is given. It may be the case that a strict adherence to 2g/kg every six weeks is not an optimal strategy. We have shown that if, over the course of a year, the amount of IVIg were reduced to an average of 1g/kg or 1.5g/kg and quality of life improvement were maintained then the cost per QALY could be reduced to below £100,000.

Policy makers have to decide how to allocate resources across and within different disease areas, and calculating costs per QALY allows comparisons to be made with interventions in other areas. Our *base case* results suggest that IVIg is not as cost-effective as the use of riluzole for motor neurone disease which has a cost per QALY of around £50,000 [20], but our sensitivity analyses show that the treatments may have more similar cost-effectiveness. However, the cost-effectiveness of IVIg does appear to be far greater than that estimated for the use of beta-interferon for multiple sclerosis which has a base case cost per QALY of around £800,000 [21]. *Clinical* comparisons are seldom made between such diseases as they are markedly different in effects, prognosis and response to therapy. *Economic* comparisons however will (often intuitively) be made, but in the absence of an economic evaluation such comparisons are uninformed.

Although the incremental cost per QALY of IVIg treatment is high, it needs to be recognised that prednisolone did not result in any quality of life improvement over the six week treatment period and therefore IVIg would be preferred in terms of QALYs gained. Prednisolone did not produce a significant change in disability compared with IVIg over the initial six-week period in the cohort of patients for whom cost-effectiveness data were available, nor was there any significant difference between prednisolone and IVIg in change in disability in the groups for whom data were available in both treatment periods of the crossover trial [12].

This study has a number of limitations. First, the potential efficiency of the cross-over design did not benefit the economic analysis due to the attrition rate and the presence of substantial baseline costs in the group initially treated with prednisolone. Second, the

sample size was small. However, there was still sufficient power to detect significant differences in costs and this was because of the low variability in costs among those patients receiving IVIg. Third, although much emphasis has been placed on changes in quality of life it is not clear how sensitive the EQ-5D is for this patient group. As a generic measure it is possible that it may miss some aspects of quality of life that are peculiar to peripheral nerve disorders. Finally, the study was relatively short-term. In order to assess the long-term comparative cost-effectiveness of IVIg and prednisolone it would be necessary to consider carefully the impact of side effects on quality of life and cost. It is thought that the side effects of IVIg treatment are generally minor [1, 22] but there is some dispute regarding their frequency. Brannagan et al [23] found that 59% of patients receiving IVIg suffered some adverse effect and Bertorini et al [24] reported a figure of 81%. However, most of these effects were transient and occurred in the period during and immediately after infusion. Aseptic meningitis has been reported in around 11% of cases [25] but treatment is usually limited to analgesics. More serious side effects such as acute renal failure and myocardial infarction have been reported but these are rare. Long-term treatment with steroids is widely recognised as causing serious side effects including osteoporosis, cataracts, diabetes, hypertension and obesity. Figures are not available for side effects associated with steroid treatment for CIDP but evidence from other areas where high doses are used may be helpful. Applying costs derived from side effects for patients who have undergone renal transplantation, and adjusting the quality of life figures, shows a modest reduction in the cost per QALY for IVIg. However, these figures are only speculative.

In conclusion, over a six-week period, treatment with IVIg was shown to be substantially more expensive than treatment with prednisolone for patients with CIDP. IVIg did not reduce physical disability significantly compared with prednisolone but did result in greater improvements in health-related quality of life and associated utility. The incremental cost per QALY of IVIg was very high but there appear to be grounds for believing that the figure would be lower over a longer time period. More work is required to understand the long term consequences of CIDP and the effects and side effects of different treatment options on service costs and outcomes.

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Table 1. Unit costs of services

	Unit of measurement	Unit cost (£ UK, 1998)	Comparative price levels			
			Belgium	Greece	Italy	Spain
		1.00[1]	1.19[1,2]	1.43[1,2]	1.79[1,3]	1.25[1,3]
Intensive care ward	Inpatient day	765	643	535	397	578
Acute ward	Inpatient day	208	175	145	201	214
Rehabilitation ward	Inpatient day	253	213	177	214	306
Neurology outpatient visit	Appointment	84	71	59	47	67
Other outpatient visit	Appointment	60	50	42	34	48
Day hospital	Attendance	103	87	72	58	82
Physiotherapist	Minute of contact	0.48	0.40	0.34	0.27	0.38
Occupational therapist	Minute of contact	0.53	0.45	0.37	0.30	0.42
General practitioner	Minute of contact	1.53	1.29	1.07	0.85	1.22
Nurse	Minute of contact	0.38	0.32	0.27	0.21	0.30
Social worker	Minute of contact	0.53	0.45	0.37	0.30	0.42
Chiropodist	Appointment	16	13.45	11.19	8.94	12.80
Other	Appointment	67	56.30	46.85	37.43	53.60
Informal care	Per hour	6.89	5.79	4.82	3.85	5.51

[1] Multiplier to adjust for exchange rate and cost of living differences using the purchasing power parity method.

[2] Ratio between purchasing power parity and exchange rate.

[3] Medical cost indices obtained from Schulman et al [14].

Table 2. Sample characteristics.

	Full sample		Sample at Period 1		Sample at Periods 1 and 2	
	P-I (n=15)	**I-P (n=17)**	**P-I (n=13)**	**I-P (n=12)**	**P-I (n=11)**	**I-P (n=5)**
Male, n (%)	9 (60)	12 (71)	9 (69)	7 (58)	7 (64)	3 (60)
Female, n (%)	6 (40)	5 (29)	4 (31)	5 (42)	4 (36)	2 (40)
Age	52.1 (18.3)	55.8 (16.2)	53.9 (17.3)	52.0 (13.6)	53.9 (18.0)	55.7 (13.9)
Illness duration	5.2 (6.5)	5.3 (7.8)	5.6 (6.9)	5.5 (8.3)	6.4 (7.2)	9.0 (10.4)
Worst arm disability grade in any attack	2.2 (1.1)	2.6 (1.4)	2.0 (1.1)	2.3 (1.3)	1.9 (1.1)	2.0 (1.9)
Worst leg disability grade in any attack	1.6 (0.8)	2.5 (1.8)	1.5 (0.5)	2.1 (1.7)	1.5 (0.5)	1.8 (1.9)
Physical disability grade at randomisation	3.5 (1.3)	4.1 (2.0)	3.5 (1.4)	3.3 (1.5)	3.5 (1.5)	3.0 (1.2)

P-I prednisolone followed by IVIg, I-P IVIg followed by prednisolone

Figures are means (standard deviations) unless stated otherwise

Table 3. Six week cost (1997-98 prices) of services for patients receiving treatment during first treatment period.

	Baseline (n=25)				*Prednisolone (n=13)*				*IVIg (n=12)*				*T-test*
	N	**%**	**Mean**	**SD**	**N**	**%**	**Mean**	**SD**	**N**	**%**	**Mean**	**SD**	**p**
In-patient	7	28	558	1790	2	15	1305	3743	0	0	0	0	0.240
Day patient	4	16	44	150	0	0	0	0	0	0	0	0	-
Out-patient	19	76	41	52	3	23	21	43	2	17	52	122	0.388
Community contact	15	60	99	439	3	23	89	280	0	0	0	0	0.280
Informal care	10	40	235	427	3	23	60	118	4	33	76	177	0.800
Treatment	-	-	-	-	13	100	5	0	12	100	2152	19	<0.001
Total	23	92	977	2297	13	100	1481	4024	12	100	2280	190	0.499

Table 4. Sensitivity analysis of incremental cost-effectiveness (IVIg minus prednisolone)

		Cost-effectiveness measure			**Cost-utility measure (QALY)**					
		Physical disability score			EQ-5D quality of life score (community values)			EQ-5D quality of life score (patient self-rated)		
		Lower-bound 95% CI	Baseline estimate	Higher-bound 95% CI	Lower-bound 95% CI	Baseline estimate	Higher-bound 95% CI	Lower-bound 95% CI	Baseline estimate	Higher-bound 95% CI
		-1.71	*-0.5*	*0.69*	*-0.05*	*0.13*	*0.3*	*-2.8*	*12.8*	*28.5*
COST										
Lower-bound 95% CI	*£700*	nd	nd	1,014	nd	46,667	20,222	nd	47,396	21,287
Baseline estimate	*£1609*	nd	nd	2,332	nd	107,267	46,482	nd	108,943	48,929
Higher-bound 95% CI	*£2185*	nd	nd	3,167	nd	145,667	63,122	nd	147,943	66,444

nd = not defined: IVIg was inferior on outcome and more expensive in cost than prednisolone, i.e. dominant.