Pharmacoeconomics of Intravenous Immunoglobulin in various Neurological Disorders

Ching-Piao Tsai

INTRODUCTION

Intravenous immunoglobulin (IVIG) has multiple actions on the immunoregulatory mechanism. Recent controlled clinical trials have shown that IVIG is effective as treatment of choice in patients with Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and multifocal motor neuropathy (MMN), and as second-line therapy for dermatomyositis, myasthenia gravis, Lambert-Eaton myasthenic syndrome, and stiff person syndrome. In paraproteinemic IgM anti-MAG (myelin-associated glycoprotein) demyelinating polyneuropathies and inclusion body myositis, there is also a remarkably good safety record for long-term administration with IVIG.

As health-care costs are increasing year by year in many western countries as well as newly developing countries, the share of drug costs in health-care costs is growing annually as well. Although new and more expensive drugs are introduced frequently, budgets are limited, and as a consequence, health-care and drug budgets are becoming increasinglyjumped. Thus, efficacy and safety are essential considerations in differentiating drugs. Although the cost of IVIG is higher than most other therapies, the other therapeutic options may cause significant long-term side effects. This has led to a reevaluation of the cost of IVIG; in addition, there are concerns regarding its safety and future availability. A single, standard 2.0 g/kg course of IVIG costs approximately 3500 and has become the major drug expenditure item in many neurology fields. Thus, pharmacoeconomic aspects of IVIG are of increasing importance.

Pharmacoeconomics measures ‘value for money’, i.e., quantifying gain in health per monetary unit, implying that results are based on clinical research involving both randomized clinical trials and observational research. Besides clinical data, decision and mathematical models are often used in pharmacoeconomics. There were three techniques for pharmacoeconomic analysis that are often used in practice: cost-benefit analysis, cost-effectiveness analysis, and cost-utility analysis. Cost-benefit analysis (CBA) is a term that refers both to helping to appraise, or assess, the case for a project, program or policy proposal and an approach to making economic decisions of any kind. Cost-effectiveness analysis (CEA) is a form of economic analysis that compares the relative costs and outcomes of two or more courses of action. CEA is distinct from CBA, which assigns a monetary value to the measure of effect. Typically the CEA is expressed in terms of a ratio where the denominator is a gain in health from a measure and the numerator is the cost associated with the health gain. Cost-utili-
Outcome assessment in neurological diseases has always been based on physician-derived and instrumental findings. Over the last two decades, clinical researchers have emphasized the need for standardized evaluation of concepts such as health related quality of life (HRQOL), which represents a further step toward an evidence-based approach to treatment of neurological disease.

Pharmacoeconomics of IVIG in Neurological Disorders

GBS, CIDP, and MMN are major immune related neuropathies, although the pathogenesis of these conditions is not yet fully understood. Costs of GBS in the United States are estimated (per patient) to be US $110,000 for direct health care and US $360,000 in lost productivity. Concerning the treatment regimen of GBS, there is no significant difference in the efficacy of treatment with IVIG, plasma exchange (PE) or PE followed by IVIG. Because of its convenience and noninvasiveness, and because IVIG has significantly fewer complications than PE (class I evidence), IVIG is now recommended as a first-line treatment option for moderate or severe GBS, to be administered within two weeks of disease onset. The effects of IVIG on immune and inflammatory processes suggest that it is an agent worthy of investigation in these diseases; both clinical and economic factors should be taken into consideration when choosing among treatment options.

There have been few published analyses of cost-effectiveness of IVIG used for neurological conditions. One study in GBS suggested that the cost of IVIG was 60% more than PE (PE, US $6,204; IVIG US $10,165). The incremental cost savings of PE treatment per patient ac compared to IVIG treatment varied from US $304 to US $6,625 depending on the IVIG product selected. This analysis showed that PE on average cost US $4,000 less per patient than IVIG. However, this study only based on secondary data and included only direct health care costs. Patients with neurological conditions are likely to receive a wide range of services, and family and friends may be involved in caring for the patient. If the use of such services can be reduced by the use of IVIG, some or all of the intervention costs may be neutralized.

Frenzen et al reported that the estimated annual cost of GBS was US $1.7 billion (95% CI, US $1.6 to US $1.9 billion), including US $0.2 billion (14%) in direct medical costs and US $1.5 billion (86%) in indirect costs. Most of the medical costs were for community hospital admissions, and most of the indirect costs were due to premature deaths. The mean cost per patient with GBS was US $318,966 (95% CI, US $278,378 to US $359,554). The economic cost of GBS was factual and was largely caused by disability and death. The cost estimate summarizes the lifetime health burden caused by GBS in monetary terms and provides some of the information needed to assess the cost-effectiveness of health measures that affect GBS.

PE has been shown to be effective in the treatment of GBS. In one study comparing PE with supportive therapy in Scandinavia, the cost of PE was achieved by the savings in health care costs as a result of shorter hospital stay. Similar conclusions have been reached in the United Kingdom. For patients with moderately severe GBS, one study calculated that four plasma exchanges are more cost-effective than two. However, a Dutch study reported a higher rate of complications with PE than IVIG; pneumonia, atelectasis, thrombosis, and hemodynamic difficulties occurred more often with PE than with IVIG. Sixteen of 73 patients (22%) had multiple complications with PE compared with 5 of 74 (7%) with IVIG. In the largest trial, adverse events occurred in 8 of 121 patients (7%) in the PE group (hypotension, septicemia, pneumonia, malaise, abnormal clotting, and hypocalcaemia) and in 6 of 130 (5%) patients in the IVIG group (vomiting, meningism, renal failure, myocardial infarction, and infusion site erythema). The increased rate of complications with PE involve increased cost, from a pharmacoeconomic perspective.

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In severe GBS, use of high-dose IVIG led to faster and more complete clinical recovery than PE. There were no adverse reactions to IVIG, and total cost was greater in patients receiving PE as a consequence of adverse reactions and complications. These preliminary results suggest that IVIG may be more beneficial and less expensive than PE in treatment of GBS (14).

In a Indian study, 25 cases were reported; all of the eight late referrals required mechanical ventilation, however, only 3 of 17 patients admitted electively required mechanical ventilation. Mean duration of pediatric intensive care unit stay in the late referrals was 27 days, compared to 15 days in the elective admissions. These results were consistent with those of previously published reports that early use of IVIG could reduce the mortality, need for intubation and mechanical ventilation, and cost (15).

Frenzen et al reported a decreased hospitalization rate for GBS in the United States. A reduction in transfers accounted for a quarter of the decrease in the GBS hospitalization rate. This reduction in transfers may reflect the shift from PE to IVIG therapy. The GBS hospitalization rate decreased 20.1% (95% CI 18.3% to 21.9%) between 1993 and 2004. This decrease affected all age groups except those aged 18-44 years. There were several changes in medical care during the period, including a shift from PE to IVIG therapy (16).

Tsai et al. also conducted a retrospective study from 1999 to 2004, which included a total of 24 patients with GBS who were admitted to Taipei Veterans General Hospital. This study showed that except for the direct costs of the drugs used in IVIG, treatment of GBS with IVIG was more cost-effective ($p = 0.057$) than that with PE due to reduced length of hospitalization and reduced cost of procedures and hospitalization. The study also showed that the total costs were higher for patients on ventilators than those not requiring ventilators ($p = 0.008$, t-test), and the length of hospitalization showed a very strong linear relationship to total costs (Pearson correlation coefficient $= 0.907$) (17).

Although the total cost of PE may be similar to that of IVIG, the QOL seems to be better after treatment with IVIG. The IVIG regimen requires an infusion every 4 to 6 weeks, which can be given even in a home-infusion setting; in contrast, PE requires catheter insertion, is associated with discomfort and more adverse effects, requires specialized staff and equipped units not always available in every hospital, and requires frequent hospitalizations, especially during the early treatment phase when 3 exchanges per week are needed (18).

Pauda et al conducted a study in 25 patients treated with IVIG to evaluate the early effects on their health-related QOL, including 8 with CIDP, 3 with GBS, 3 with multifocal motor neuropathy, 1 with multineuropathy of cranial nerves, and 10 with myasthenia gravis. After IVIG treatment, the patients reported less physical dysfunction, less pain, less fatigue, and better function of the upper limbs. However, there was no improvement in the scales of psychological distress and in social and role disability due to emotional problems. The data suggest that physical aspects of patients’ health-related QOL may show early improvement after administration of IVIG, concomitant with improvement in muscle strength, but without a beneficial effect on the emotional aspects (19,20).

In treating CIDP, corticosteroids, IVIG, and PE are equally effective. Despite the high costs and relative lack of availability, IVIG is preferentially used. For the one-third of patients who do not respond, other immunosuppressive options are available. A Cochrane review of treatment of CIDP evaluated five randomized controlled trials involving 113 patients with CIDP. The report confirmed significantly more short term improvement in disability with IVIG than placebo. Crossover trials showed no significant differences comparing IVIG with PE or oral prednisolone (21-23).

In comparing IVIG and prednisolone in treatment of CIDP, IVIG is clearly most costly in the short term. However, for patients treated with prednisone alone for more than 2 to 3 years, irreversible adverse steroid effects (osteoporosis, cataracts, diabetes, hypertension, obesity, avascular necrosis of the hip), seemingly incomplete response, frequent physician visits, time lost from work, and QOL issues may make the true cost comparable with that of IVIG (24).

Preliminary data on CIDP from a double-blind study...
comparing IVIG to steroids showed that during the short 6-week study period, IVIG was substantially more costly than prednisone, but scores on the EuroQoL instrument increased more in the IVIG group than the prednisone group. Whether in the long run the mean annual health care costs of such steroid-related adverse effects and apparent reduction in QOL will compensate the cost difference between IVIG and prednisone needs to be determined with careful long-term cost-utility analyses.

Using a net-benefit approach, it was shown that the probability of IVIG being cost-effective in comparison with prednisolone was 0.5 or above (i.e., was more likely to be cost-effective than cost-ineffective) only if one quality adjusted life year (QALY) was valued greater than €250,000. The cost-effectiveness of IVIG is greatly affected by the price of IVIG and the amount administered. The impact of later side effects of prednisolone on long-term costs and quality of life are likely to increase its long term costs and to reduce the incremental cost per QALY of IVIG treatment as compared to prednisolone treatment.

The cost per QALY of IVIG compared with oral prednisolone is high. While IVIG is recommended for the treatment of CIDP, for reasons of cost and convenience steroids may be preferred as first-line treatment, and IVIG reserved for treatment failures or cases in which steroid side-effects are troublesome or anticipated (25). Patients with pure motor CIDP may deteriorate after steroids; for this group of patients, IVIG is the first choice (26).

CIDP patients should be informed of the advantages and disadvantages of IVIG and steroids treatments and be involved in the choice of treatment, based on the judgment of the cost-effectiveness analysis of IVIG or alternative treatments (27,28).

In MMN, four randomised controlled trials including a total of 34 patients were suitable for a systematic review; strength improved in 78% of patients treated with IVIG and only 4% of placebo-treated patients. Disability improved in 39% of patients after IVIG and in 11% after placebo (difference not statistically significant). Mild, transient side effects were reported in 71% of IVIG treated patients, but serious side effects were not encountered (29). IVIG is the treatment of choice for MMN, but inadequate response in 20% of the patients plus the high cost and variable availability of IVIG show the need for the search of adjunctive immunosuppressive therapies (30).

CONCLUSION

Although IVIG is expensive, we believe it is cost-effective based on its impact on the course of GBS because it shortens hospital stay and duration of mechanical ventilation, and it reduces the chance of long-term disability and inability to work in treating GBS as compared with treatment with PE, the total cost of PE may be similar or lower than that of IVIG, however, the QOL seems to be better after treatment with IVIG.

In cases of CIDP, Many studies have shown similar effectiveness with the treatment of PE and IVIG. IVIG clearly provides less patient discomfort and greater ease of drug administration than PE. Although IVIG is initially more costly than prednisone, the adverse and irreversible side effects of prolonged steroid use may offset initial differences in cost.

Despite the high cost of IVIG, pharmacoeconomic data suggest that its convenience, cost-reduction and improved QOL make it an appealing therapeutic approach; however, a larger scale prospective study in the context of pharmacoeconomic analyses remain to be investigated.

REFERENCES
