ORIGINAL ARTICLE

Home IVIG for CIDP: A Focus on Patient Centred Care

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ABSTRACT: ***Objective:*** To determine the safety and tolerability of home-based intravenous immunoglobulin (IVIG) (Gamunex) as maintenance treatment in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in Canada. ***Methods:*** We enrolled ten subjects with CIDP who had previously received IVIG in the hospital setting to receive the comparable IVIG dose (1-2 g/kg/month) in the home for six months. The patients were evaluated in the clinic at three months and at six months to evaluate their clinical status as well as the safety and tolerability of IVIG. ***Results:*** All subjects tolerated home-based IVIG treatment as maintenance treatment of CIDP. There were no serious adverse events related to IVIG. Subjects did experience "anticipated" IVIG events post-infusion such as headache and fatigue, which were managed with analgesics and supportive counseling. One subject withdrew consent at end of study due to hospitalization. This event was not related to the IVIG. Another subject experienced a "flare" of CIDP symptoms near the end of the study, however, completed all visits as per protocol. All subjects expressed excellent satisfaction with the individualized therapy, and almost all (nine out of ten) patients preferred home-infusion to hospital-infusion. ***Conclusion:*** Intravenous immunoglobulin can be delivered safely and is well tolerated outside the hospital setting in Canada in patients with chronic, stable neuromuscular conditions such as CIDP who have previously tolerated IVIG in the hospital Medical Day Care Unit.

RÉSUMÉ: Administration de l'immunoglobuline intraveineuse à domicile pour traiter les patients atteints de polyradiculoneuropathie démyélinisante inflammatoire chronique : soins axés sur le patient. ***Objectif :*** Le but de l'étude était de déterminer la sécurité et la tolérabilité de l'administration d'immunoglobuline intraveineuse (IGIV) [Gamunex] comme traitement d'entretien chez des patients atteints de polyradiculoneuropathie démyélinisante inflammatoire chronique (PDIC) au Canada. ***Méthode :*** Nous avons recruté 10 sujets atteints de PDIC qui avaient reçu de l'IGIV antérieurement en milieu hospitalier afin qu'ils reçoivent une dose comparable d'IGIV (1-2 g/kg/mois) à domicile pendant 6 mois. Les patients étaient examinés à la clinique après 3 et 6 mois de traitement pour évaluer leur état clinique ainsi que la sécurité et la tolérabilité de l'IGIV. ***Résultats :*** Tous les sujets ont bien toléré le traitement à domicile par l'IGIV comme traitement d'entretien de la PDIC. Il n'y a eu aucun incident thérapeutique sérieux relié à l'IGIV. Les sujets ont présenté des incidents thérapeutiques concordant avec le profil d'innocuité connu du médicament après l'infusion tels la céphalée et la fatigue qui ont été traités par des analgésiques et un counseling de soutien. Un sujet s'est retiré de l'étude à la fin de celle-ci parce qu'il a dû être hospitalisé. Cet incident n'était pas en lien avec l'IGIV. Un autre sujet a présenté une poussée de symptômes de PDIC vers la fin de l'étude. Il a cependant complété toutes les visites de suivi prévues au protocole. Tous les sujets ont témoigné d'un haut niveau de satisfaction de cette thérapie individualisée et presque tous (9 sur 10 sujets) ont préféré l'infusion à domicile plutôt qu'en milieu hospitalier. ***Conclusion :*** L'IGIV peut être administrée sans danger en dehors du milieu hospitalier au Canada et ce traitement est bien toléré chez les patients atteints de pathologies neuromusculaires chroniques stables telles la PDIC qui ont bien toléré l'IGIV à l'unité de jour en milieu hospitalier antérieurement.

Can J Neurol Sci. 2013; 40: 384-388

Intravenous immunoglobulin (IVIG) is an effective treatment for chronic inflammatory demyelinating polyradiculopolyneuropathy (CIDP)[1,2] and has recently obtained a formal designation as an approved treatment for the disease in Canada[3]. Although home-based IVIG for treatment of neuromuscular conditions has been used extensively for many years in the United States and Europe[4,5], it is currently only available in Canada through infusion in the hospital setting. More recently, subcutaneous immunoglobulin (SCIG) formulations have been used elsewhere in the world in patients with neuromuscular conditions, signaling a potential phase-shift in the way immunoglobulins are administered for these conditions[6-8].

Home-based IVIG treatment offers potential benefits to patients and also helps to alleviate significant health care utilization stressors. One of the obvious benefits is convenience to patients, who can avoid significant traveling time and costs[9]. Home IVIG also results in improved availability of hospital resources for treatment of patients with other neurological, hematological and immunological conditions with other blood and non-blood products[10,11]. Increased utilization of IVIG coupled with limited availability in hospital units poses challenges for administration of IVIG under the current model. In many Canadian jurisdictions, limited access to hospital beds or chairs in medical day units, which are frequently used for other infusions or procedures, has impacted the safety of patients with immune-mediated neuromuscular conditions as timely treatments cannot be accommodated. Home IVIG treatment

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Received August 23, 2012. Final Revisions Submitted November 14, 2012.

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holds promise to ensure equal access to appropriate care for neuromuscular patients in Canada.

Implementation of an out-of-hospital IVIG system needs to contain protocols for handling potential complications of therapy, both minor, such as headache and fever, and major, such as hemolysis, renal toxicity, cardiovascular events and severe allergic reactions[12]. Nurses with specialized training and protocols specific to patients with neuromuscular disorders are necessary[13]. Safety data as well as home-nursing protocols for use of IVIG from other countries have been published[14,15].

We aimed to determine the safety and tolerability of home-based IVIG (Gamunex) as maintenance treatment in patients with CIDP in Canada.

Methods

Patients

Patients with CIDP being treated with IVIG and followed in the neuromuscular clinic at Toronto General Hospital (TGH), University Health Network, were eligible for the study. Patients with a confirmed diagnosis of CIDP based on the Koski criteria[16] were eligible for the study. Patients were included if they had had a diagnosis of CIDP for at least three months and had at least one treatment with IVIG in hospital without major complications. Patients were excluded from the study if they had previously experienced a serious adverse reaction from IVIG, had known IgA deficiency or any other serious medical, or psychiatric disorders which would interfere with the patient's ability to participate in the study or interfere with study assessment. The Research Ethics Board of the University Health Network approved the study. All subjects provided informed consent prior to having any study procedures. All study procedures followed the standards set by the Declaration of Helsinki.

Baseline Assessments

The following baseline assessments were done within two weeks of screening: 1) inflammatory neuropathy cause and treatment (INCAT) disability score, a 10 point disability scale validated in the inflammatory neuropathy research[17] 2) grip strength as determined using a Jamar dynamometer (Lafayette Instruments, Lafayette, Indiana, USA) 3) Medical Research Council (MRC) sum score 4) SF-36 Quality of Life (QOL) Index. During the initial baseline assessment, a one-hour training module with the patient or designated adult caregiver was performed to review the home infusion study procedures.

Nursing

A research nurse with previous home care experience performed the infusions. Blood bank staff provided supplemental training in the handling and transportation of blood products. Vascular access was reviewed and competency achieved. Hospital policy mandated advanced cardiac life support (ACLS) training for study purposes although basic CPR is the mandate for health care providers.

IVIG Preparation and Home Infusion

Prior to the home visit, the blood bank dispensed the IVIG directly to the research nurse after the doctor's orders and prescription were crosschecked by two lab personnel and the research nurse. The IVIG was packaged in a validated, temperature-controlled cooler (monitored via a thermometer).

Once in the home, the patient was pre-medicated with oral acetaminophen 625 mg and diphenhydramine 50 mg. Venous access was achieved and baseline vital signs taken. The IVIG was administered as per standard protocol. The vital signs and patient's general well-being were monitored throughout the infusion. Any untoward events or unanticipated side effects were reported to the principal investigator and to the blood bank. Once the infusion was complete, the IV was discontinued and the patient was monitored for another 30 minutes to ensure that the patient was stable. The nurse provided the patient with a direct contact number in case of any concern. All study materials were returned to the blood bank.

Mid and end-of-study assessments

All the subjects had clinic evaluations after the third and sixth infusions, which included neurological examination, INCAT assessment, grip strength, MRC sum score, SF-36 QOL assessment and review of adverse events and tolerability. All patients completed a 16-question patient satisfaction questionnaire designed by the study team to address issues specific to the home IVIG infusions. Four questions in each of the following categories: access and convenience, comfort, perception of safety, and assessment of nursing, were graded on a scale of 1 (poor) to 5 (great) for a total score of 80. At the end of the study, patients were also asked whether they preferred home or hospital infusion, as well as the reason for their selection.

Statistical Methods

This is a pilot study of home IVIG infusion and was not adequately powered to prove efficacy of any particular therapy for CIDP. Descriptive statistics were used to report adverse events, changes in INCAT, SF-36 QOL, grip strength, and MRC motor sum score when applicable.

Results

Patient demographics are presented in Table 1. Ten subjects (six male, four female) ranging in age from 26 to 81 were included in the study. All had been diagnosed with CIDP (duration of disease 3 -192 months) and had previously received IVIG by infusion in the medical day unit of the hospital (range 1 – 180 months). Doses ranged from 54 to 140 grams per treatment cycle (1-2 g / kg) dosed every three to four weeks as per their protocols in the medical day unit. Infusion times at home averaged six hours with a range from four hours to ten hours in a patient who was a difficult IV start and who experienced severe headaches at faster infusion rates.

Nine subjects completed the six-month study; one subject exited the study early due to a serious adverse event that was unrelated to IVIG (polypharmacy with pain medications for arthritis leading to brief hospitalization). No serious reactions related to IVIG were identified in any of the patients in the study. Subjects did experience minor side effects with IVIG infusions and these were managed with analgesia and supportive counseling. Mild headaches occurred most commonly in 7/10

Table 1: Patient demographics

Patient No.	Age	Gender	Disease Duration (months)	Duration IVIG therapy (months)
1	49	Female	36	12
2	52	Male	192	180
3	42	Female	72	48
4	81	Male	24	9
5	40	Female	2	1
6	40	Male	7	3
7	26	Male	12	6
8	80	Female	108	96
9	39	Male	3	1
10	58	Male	3	1

patients (85.7% of all infusions) during the study. Other common side effects were nausea and leg heaviness, each occurring in 12.2% of all infusions. One patient complained of a hoarse voice during one infusion, which was considered as possibly related to IVIG. Treatment was not stopped. One patient had transient, mild flank pain during two infusions, similar to symptoms experienced during previous hospital-based infusions; this pain did not occur during the other four home infusions.

Clinical outcomes remained stable in nine out of ten patients, with only one subject experiencing a worsening of CIDP symptoms near the end of the study that required treatment with prednisone 1 mg / kg to stabilize the patient in addition to the IVIG treatments. The INCAT score remained stable or improved in all patients from baseline compared to end of study (mean 2.6 vs. 1.8 points, p=0.33). The MRC sum score also remained stable at end of study compared to the beginning of the study (mean 78.6 vs. 75.2 points, p=0.45) as did the Jamar hand grip (mean 23.4 vs. 28.1 kg right hand, p=0.23 and mean 21.5 vs. 27.1 kg left hand, p=0.19). The SF-36 also showed no significant change in six months: mean 38.4 vs. 39.6 pts, p=0.76 in physical domains (score / 100) and 35.7 vs. 35.3, p=0.89 in mental domains (score / 100).

Patient satisfaction and preferences, including reasons for preference, are listed in Table 2. All subjects expressed satisfaction with the individualized therapy, increased autonomy in management of their own health care, minimization of difficult commutes and time spent in the hospital. Patient satisfaction with home infusion was excellent (≥75/80) in all patients. Nine out of ten patients preferred home infusion versus hospital-based infusion. One patient found it inconvenient to confine her dog to a crate for the duration of the nursing visit.

Formal cost analysis and quality adjusted life years were not done in this pilot study, but a simple comparison of costs per patient showed that blood bank related costs, administrative fees and supplies were the same for both hospital and home IVIG treatments. Nursing costs in the medical day unit were higher than for the research nurse, but the 1:1 nurse-to-patient ratio for home infusion (compared to approximately 1:4 for hospital therapy) makes this a more costly therapy with respect to nursing overall. Travel costs could not be compared reliably due to lack

Table 2: Patient satisfaction and preferences

Patient No.	Patient Satisfaction	Hospital/Home Preference	Reason for Preference
1	75/80	Hospital	Pet care difficult at home during home-infusion
2	79/80	Home	Ability to work from home
3	80/80	Home	Distance travel and child care arrangements
4	80/80	Home	Age and mobility; dependence on care-giver for transportation
5	79/80	Home	Convenience and dependence on others for transportation
6	78/80	Home	Dependence on spouse for transportation
7	80/80	Home	Compliance to treatment
8	80/80	Home	Age, mobility and dependence on others for transportation
9	80/80	Home	Ability to work from home
10	80/80	Home	Ability to work from home

https://doi.org/10.1017/S0317167100014359 Published online by Cambridge University Press

of information related to patient transportation costs for hospital-based infusions.

Discussion

Our results demonstrate that home-based IVIG is safe and well tolerated as maintenance treatment in a select group of our patients with CIDP. To our knowledge, this is the first such study performed in Canada. All of the patients were very satisfied and supportive of the home IVIG program and 90% of patients preferred home infusion to hospital-based treatment.

The safety and tolerability of home IVIG in our patients is consistent with many years of similar experience in other countries. In the United States (US), several publications have recently outlined the safety profile of home IVIG for treatment of neuromuscular conditions in large populations[18]. Although not universally available throughout Europe, England and Denmark have well-established out-of-hospital IVIG infusion programs with data demonstrating similar safety[19,20]. In line with protocols in these countries, our study required close monitoring during and after infusion for a brief period of time. In the current study, patients encountered anticipated, minor reactions which were easily managed and we did not observe any serious adverse reactions related to IVIG. It is not possible to make any comment on the prevalence of serious adverse events related to IVIG in our small group of patients.

In selecting subjects for this study, we aimed to choose a representative sample of patients with chronic, stable neuromuscular disease on IVIG treatment. As such, patients in the study were diverse in age, disease severity and dose of IVIG required. During the study, patients varied with respect to disease activity, but most were stable or improved. A single patient worsened and required additional immunosuppressive medication. The ability to continue home IVIG infusion without compromising this patient's care suggests that out-of-hospital IVIG is safe and feasible in a "real-world" clinical setting, where patients can deteriorate despite active treatment.

Patient satisfaction with home-infusion was high in all cases; 90% favoured this treatment over hospital infusion. Again this observation is consistent with experience in the US and England, where home infusion is commonplace and where self-administered IVIG infusion protocols are in place[4,21]. In our study, patients preferred home infusion due to the ability to work from home in the younger patients and relief from travel to hospital, particularly in the elderly patients. An additional benefit was compliance with treatment, as travel to the hospital posed a major barrier for one of the younger patients. After entering the home infusion study, compliance was 100%. It is important to note that not all patients preferred home infusion. The one patient who found it difficult to modify the home setting for IVIG treatments serves as a reminder that patient-centered care should be the priority when electing treatments in our patients. Some patients may prefer the socializing and perceived security of infusion in a hospital day unit.

None of the clinical outcome measures were significantly different from the start to end of study (INCAT, MRC and Jamar hand grip strength), and this is not unexpected as our study was not powered to detect these changes. SF-36 QOL also remained stable, but is not an ideal inflammatory neuropathy specific measure of QOL. Since all patients going into the study were stable, finding no significant changes in the clinical outcome measures is not unexpected.

It is important to note the limitations of our study. It is a small patient population of patients with stable CIDP on treatment. All had received initial treatment with IVIG in hospital and so were expected to tolerate the treatment in the home. Based on this study, we would administer the initial IVIG in a hospital unit and then consider home IVIG, although in other countries, patients are often treated with home IVIG as first line therapy. Patients with less stable neuromuscular disorders such as myasthenia gravis (MG) may be more challenging to treat in the home due to the potential requirement for respiratory support. Although home infusion is used routinely in countries such as the US for management of MG[22], starting with stable CIDP patients on chronic IVIG makes more sense in Canada where experience is limited. Our article also does not address all logistical aspects of out-of-hospital infusion, including mechanisms to deliver immunoglobulin to the home or infusion centre or track the product outside the setting of a research study. As release and tracking of immunoglobulin product is already routine in other conditions such as primary immune deficiency, this may serve as a model to address these issues[23,24].

In most countries, nursing costs associated with the infusion are not covered by the company making the product but rather by third party payers or government sponsored programs. As such, there are cost concerns with home-infusion as the sole method of out-of-hospital IVIG treatment, particularly given the costs associated with 1:1 nursing. In spite of this, economic comparisons have shown that home-based IVIG may actually be significantly cost saving compared to hospital-based treatment[25].

In order to maximize nursing ratios, existing medical treatment pods available in some jurisdictions through provincial community access care centres could also serve as more cost-effective delivery system, immobile or immunosuppressed patients are obvious candidates for actual home IVIG infusion in the current model. New treatments including SCIG are also currently being investigated[26]. If SCIG is proven to be an efficacious treatment for inflammatory neuromuscular conditions such as CIDP and MMN, this offers yet another option for patients to administer treatment at home. Although they require more frequent but shorter self-administered infusions, they do increase patient autonomy and have also shown cost-benefit in other conditions such as primary immune deficiency[25].

As health care resources continue to be increasingly scarce in Canada, alternative rational and cost-effective treatments and delivery methods are critical, especially as new therapies emerge. We encourage all neuromuscular physicians in Canada to help develop out-of-hospital treatment programs, with common standards and protocols, to improve access to care for neuromuscular patients.

Acknowledgements

This study, including support for the study nurse administering IVIG was funded by an unrestricted educational grant from Grifols Canada. The authors thank Crescent Healthcare Inc (now Walgreens) for their support in developing the home infusion protocols used in this study and also the TGH Blood Bank for their support and help with the study procedures.

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