Original Article

A Retrospective Review of Real-life Practice of Intravenous Immunoglobulin Usage in Autoimmune Neurological Disease

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Abstract

OBJECTIVES: To review the prescription of Intravenous immunoglobulin (IVIg) in neurological disease regarding its efficacy, prescription pattern, indication and treatment outcome.

MATERIALS AND METHODS: We studied IVIg usage and treatment outcomes by reviewing the prescription database and medical records from 2013 to 2019 at Thammasat University Hospital (TUH), which is the university hospital in the lower central region of Thailand, and records at Bangkok International Hospital (BIH), part of the largest private hospital network in Thailand.

RESULTS: IVIg was used in 28 patients in TUH and 86 patients in BIH. The diagnoses were Guillain-Barré syndrome (GBS) (50%), myasthenia gravis (MG) crisis (23%) and chronic inflammatory demyelinating polyneuropathy (CIDP) (6%). 39.5% of patients were prescribed IVIg apart from those prescribed in line with the Thailand national list of essential medicine (NLEM) indication. The major cause of NLEM deviation is usage beyond reimbursement guidelines, but the dose of IVIg administered is within standard guidelines. IVIg usage and treatment outcomes were similar in both hospitals in the case of GBS and MG. Both groups show beneficial outcomes from IVIg. BIH used IVIg often as first line treatment for CIDP, but TUH used IVIg as subsequent therapy after failure of corticosteroid administration. TUH preferred plasmapheresis combined with a high dose steroid for neuromyelitis optica spectrum disorder (NMOSD) and autoimmune encephalitis reflecting the cost of therapy and reimbursement guidelines.

CONCLUSION: IVIg is still the mainstay treatment of GBS and MG crisis in Thailand. The outcome of GBS and MG crisis is similar in both hospitals. Private hospitals seem to have more off label use and often used IVIg as a first line therapy in CIDP, NMOSD and autoimmune encephalitis. Reimbursement guidelines and NLEM have a major impact on prescription patterns.

Keywords: IVIg, Thailand, NLEM, efficacy, indication

Human normal immunoglobulin (IVIg) is extracted from plasma pooled from more than 10,000 blood or plasma donations, of which 95% consists of IgG. Immunoglobulin G molecules consists of two functional domains, Antigen binding fragment 2(Fab2) and Fragment crystallizable (Fc). The mode of action of IVIg in neurological disease is unclear but is has been proposed as an upregulation of the inhibitory FcγRIIB[1]. US FDA approved indications for IVIg are GBS, CIDP, multifocal motor neuropathy (MMN), MG crisis, dermatomyositis and stiff-person syndrome with class I evidence.[1, 2] According to NLEM in Thailand, IVIg is approved in GBS, CIDP, dermatomyositis and MG crisis.[3] The evidence of efficacy of IVIg is summarized in Table 1.

There is much less data of the efficacy of IVIg in other diseases such as NMOSD or autoimmune encephalitis, as findings are based on small clinical trials and expert opinion. Most usage is off label.[2] Due to the high cost of treatment, the possibility of adverse drug reaction and frequent shortages,

Table 1: Efficacy of intravenous IgG in neurological disease; evidence from clinical trials.[1]

Indication	Level of evidence
Guillain-Barré syndrome	Class I
Chronic inflammatory demyelinating polyneuropathy	Class I
Multifocal motor neuropathy	Class I
Myasthenia gravis	Class I for short term efficacy; long term efficacy has not been established.
Dermatomyositis	Class I
Stiff person syndrome	Class I
Neuromyelitis Optica spectrum disorder	Class IV
Autoimmune encephalitis	Class IV
Polymyositis	Class IV
Reflex sympathetic dystrophy	Class IV
Necrotizing autoimmune myositis	Class IV
Multiple sclerosis	Class I (not effective)
Alzheimer disease	Class I (not effective)
Anti-MAG paraproteinemic neuropathy	Class I (not effective)
Inclusion body myositis	Class I (not effective)
Postpolio syndrome	Class I for short-term efficacy (not effective)

the use of IVIg should be examined carefully to minimize its misuse. Therefore, we reviewed the prescription of IVIg in autoimmune neurological diseases such as MG, GBS, CIDP, dermatomyositis, autoimmune encephalitis and other neurological diseases at TUH in Pathum Thani Thailand, which is a university hospital in lower central region of Thailand, and at BIH, which is the largest private hospital network in Bangkok in terms of efficacy and usage indication. This data will be advantageous in promoting rational drug use and future treatment uses of IVIg.

Material and Method

This is retrospective study. Data was collected retrospectively from IVIg prescription from the pharmacy database from 2013 to 2019.

Inclusion criteria are patient age >18 years, diagnosis with GBS, MG, CIDP, dermatomyositis, autoimmune encephalitis and other neurological diseases treated with IVIg at TUH and BIH.

The exclusion criteria are incomplete or missing medical records or lost follow up. This study was approved by the institutional review boards of both institutions.

Data collection

All data were collected retrospectively. We searched the prescription of IVIg of all patients in both hospitals and reviewed the diagnosis, clinical data and outcome of treatment. We collected data about age, gender, duration of symptoms, severity, IVIg dosage, other drugs and dosage, length of hospital stays, length of ICU stays, length of respiration support and outcomes of treatment. Medical Research Council (MRC) sum score was collected in GBS and CIDP, Inflammatory Neuropathy Cause and Treatment (INCAT) disability score was collected in CIDP, MG composite score (MGC) was collected in MG, and modified Rankin scale (mRS) was collected in all patients.

Definition and clinical outcomes

Guillain-Barré syndrome

Efficacy of IVIg in GBS is hastening time to unaided walking and discontinuation of ventilator compared with placebo.[4,5] IVIg appears to be useful in GBS variant but no controlled trial was conducted.[2] Indication of IVIg in Thai NLEM is severe weakness such as GBS disability scale ≥ 3. Good outcome was determined at 6 months as a GBS disability scale <3 or patient can walk unaided.[3] The modified Erasmus GBS Outcome (mEGOS) score (calculated by MRC score, Age, previous diarrhea in 30 days) >5 at admission an > 7 at 7 days after admission are associated with poor prognosis.[6,7] We used GBS disability scale <3 (walking unaided) as a favorable outcome.

CIDP

High dose steroid, plasmapheresis and IVIg are equally effective as first line treatment, at least on a short-term basis.[8-12] IVIg becomes effective at 6 weeks after treatment and maintenance infusion is needed every 4-6 weeks to prevent relapsing of disease.[13, 14] IVIg is approved in MMN[2], but it is not reimbursed in MMN in NLEM. Indication of IVIg usage in NLEM is as a second line drug in moderate classic CIDP, based on EFNS/PNS guideline 2010. The patient must have been on steroids or immunosuppressive drug usage for at least one month or the patient must have a contraindication for immunosuppressive drug or inadequate to response or severe side effects. The effective treatment outcome is assessed on improvement of INCAT disability score ≥ 1 at 6 months.[3]

MG

Acute severe exacerbations of MG were defined as diffuse extremity paresis, dysarthria, dysphagia or shortness of breath; any of these affects daily living activities.[15] IVIg and plasmapheresis are equally effective for MG crisis.[16-19] Indication of IVIg usage in NLEM is MG crisis. In this study, we used MGC instead of Quantitative MG (QMG) score due to lack of data in vital capacity and hand grip strength.

Dermatomyositis

Regarding dermatomyositis, the indications of IVIg usage in NLEM are severe life-threatening weakness, failure of high dose steroid, adverse effect of steroid usage or contraindication in steroids.[20, 21]

Autoimmune encephalitis

In autoimmune encephalitis, Thai NLEM does not include IVIg in this disease due to lack of class I evidence or supported guidelines.

Statistical Analysis

Statistical analysis was performed using SPSS (IBM SPSS statistics version 22.0.0.0). Categorical variables of baseline characteristics were presented as frequency (%) and continuous variables as means with standard variations. The baseline variables between patients from different hospital were compared using unpaired T-test. Chi square or Fisher's exact test were performed to compare proportions. Paired T-Test was performed to compare MRC and GBS disability scale to evaluate treatment effect. $p < 0.05$ was considered statistically significant.

Results

The total number of patients prescribed IVIg in TUH during the period of 2013-2019 was 243 patients. A total of 211 patients were excluded, 115 were younger than eighteen years old, 96 patients presented non-neurological disease and there was missing data in 3 patients. In the final dataset, 28 patients from TUH were included in our study. On the other hand, the total number of patients who were prescribed IVIg at BIH during the same time period were 329 patients. A total of 243 patients were excluded, 152 were younger than eighteen years old, and 91 patients presented with non-neurological disease. Therefore 86 patients from BIH were included in our study. The baseline demographic, diagnosis and IVIg dosage are summarized in Table 2. There is no difference in baseline data, diagnosis and IVIg dosage between the two groups.

IVIg was used in GBS (50%), MG crisis (23%), CIDP (6%) and other neurological diseases. Three patients from TUH and 37 patients from BIH were prescribed IVIg outside NLEM indication; One (2%) was end stage cancer, twenty-one (56%) used off label NLEM and fifteen (44%) had not fulfilled reimbursement criteria in NLEM. In summary, off label indications are often used in private practice and are non-reimbursable per NLEM criteria.

Table 2: Baseline demographic data between the two hospitals (TUH and BIH).

	Total n = 114	TUH n = 28	BIH n = 86	*p*
Gender				0.662
Male	66 (57.9)	15 (53.6)	51 (59.3)	
Female	48 (42.1)	13 (46.4)	35 (40.7)	
Age (years)	50.43 ± 17.848	47.75 ± 18.759	51.3 ± 17.567	0.363
Diagnosis				0.071
GBS	58 (50.9)	13 (46.4)	45 (52.3)	
MG	27 (23.7)	13 (46.4)	14 (16.3)	
CIDP	7 (6.1)	0	7 (8.1)	
ALS	2 (5.3)	1 (3.6)	1 (1.2)	
MMN	1 (0.9)	0	1 (1.2)	
IgM MGUS	1(0.9)	0	1 (1.2)	
Autoimmune encephalitis	6 (5.3)	1 (3.6)	5 (5.8)	
NMOSD	4 (3.5)	0	4 (4.7)	
Mononeuritis multiplex	1 (0.9)	0	1 (1.2)	
Dermatomyositis	1 (0.9)	0	1 (1.2)	
SNHL	2 (1.8)	0	2 (2.3)	
Postherpatic neuralgia	1 (0.9)	0	1 (1.2)	
Trigeminal neuralgia	1 (0.9)	0	1 (1.2)	
HSV radiculomyelitis	1 (0.9)	0	1 (1.2)	
IVIg Dosage (g/kg)				0.160
0.4	1 (0.9)	0	1 (1.2)	
0.5	9 (7.9)	0	9 (10.5)	
1	12 (10.5)	5 (17.9)	7 (8.1)	
2	92 (80.7)	23 (82.1)	69 (80.2)	
NLEM				0.005
Yes	77 (67.5)	25 (89.3)	52 (60.5)	
No	37 (32.5)	3 (10.7)	34 (39.5)	
Cause of deviation				
Terminally ill	1 (2.7)	1 (33.3)	0	
No data in NLEM	21 (56.75)	2 (66.6)	19 (55.9)	
Data in NLEM but not fulfill indication	15 (40.54)	0	15 (44.1)	

Abbreviations: IVIg= Intravenous immunoglobulin; TUH = Thammasat University hospital; BIH = Bangkok International hospital ; GBS = Guillain-Barré syndrome; MG = Myasthenia Gravis; CIDP = chronic inflammatory demyelinating polyneuropathy ; ALS = amyotrophic Lateral Sclerosis; MMN = multifocal motor neuropathy; MGUS= monoclonal gammopathy of unknown significance; NMOSD = Neuromyelitis Optica spectrum disorder; SNHL = Sensorineural hearing loss; HSV = Herpes simplex virus; NLEM= National list of essential medicine

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GBS

Fifty-eight patients were diagnosed with GBS. Forty-one patients (70.7%) were male and the mean age of patient was 49 years. Three patients were lost at follow up at 6 months and one patient died due to hospital-acquired pneumonia. Ten patients were treated with IVIg after disease onset of more than 14 days and five patients were treated with IVIg after disease onset of more than 28 days. All patients were prescribed IVIg dosage 2 g/kg. Patients who were treated with IVIg within 14 days after disease onset had greater Medical Research Council (mRC) sum score at day 7 and good favorable outcomes at 6 months. The mEGOS score ≥ 5 at admission and mEGOS score ≥ 7 at 7 days after admission were associated with poor outcomes. Demographic data of GBS patient is shown in Table 3. There was no significant difference in baseline data. Regarding the outcome of treatment, we combined the data from the two hospitals as shown in Table 4. GBS disability scale at admission compared with 6 months is shown in Figure 1. Association of mEGOS score and poor outcome at 6 months is shown in Table 5. The usage of IVIg outside NLEM reimbursement criteria included the onset of more than twenty-eight days and mild symptoms (GBS disability scale < 3).

Table 3: Baseline demographic data and treatment outcomes in GBS patients between two hospitals (TUH and BIH).

Indication	Total n = 114	TUH n = 28	BIH n = 86	*p*
Gender				0.494
Male	41 (70.7)	8 (61.5)	33 (73.3)	
Female	17 (29.3)	5 (38.5)	12 (26.6)	
Age (years)	49.72 ± 18.012	47.69 ± 20.882	50.31 ± 17.315	0.648
Duration of disease (days)	10.05 ± 16.628	5.92 ± 2.813	11.24 ± 18.696	0.314
Duration of disease (weeks)				0.594
< 4	53 (91.37)	13 (100)	40 (88.9)	
> 4	5 (8.62)	0	5 (11.1)	
AIDP subtype				0.134
Classical GBS	42 (72.41)	10 (76.9)	32 (71.1)	
MFS	4 (6.89)	2 (15.4)	2 (4.4)	
AMAN	9 (15.52)	0	9 (20)	
AMSAN	1 (1.72)	1 (7.7)	0	
Paralytic	1 (1.72)	0	1 (2.2)	
GBS disability scale				0.810
0	1 (1.7)	0	1 (2.2)	
1	0	0	0	
2	3 (5.2)	1 (7.7)	2 (4.4)	
3	24 (41.4)	4 (30.8)	20 (44.4)	
4	21 (36.2)	5 (38.5)	16 (35.6)	
5	9 (15.5)	3 (23.1)	6 (13.3)	
mRC sum score	39.71 ±15.202	39.08 ± 11.124	39.89 ± 16.293	0.867
mEGOS score at admission	3.97 ± 2.561	4.15 ± 2.703	3.91 ± 2.548	0.766
IVIg Use				
Day from symptoms onset	12.26 ± 18.808	9.08 ± 2.985	13.18 ± 21.260	0.494
Outcome Of treatment				
Days of intubation	14.73 ± 11.782	11.67 ± 6.11 (3)	15.88 ± 13.495 (8)	0.624
Days of admission	13.38 ± 11.352	12.92 ± 10.696	13.51 ± 11.648	0.871
GBS disability scale at 6 months				0.156
0	28 (50.91)	7 (58.3)	21 (51.2)	
1	8 (14.54)	3 (23.1)	5 (12.2)	
2	6 (10.91)	0	6 (14.6)	
3	5 (9.1)	1 (7.7)	4 (9.8)	
4	4 (7.27)	1 (7.7)	3 (7.3)	
5	2 (3.6)	0	2 (4.9)	
6	1 (1.8)	1 (7.7)	0	
NLEM				0.602
Yes	48 (82.76)	13 (100)	35 (77.8)	
No	10 (17.24)	0	10 (22.2)	
Cause of deviation				
Onset > 28 days	5 (50)	0	5 (50)	
GBS disability scale at onsets < 3	4 (40)	0	4 (40)	
No definite diagnosis	1 (10)	0	1 (10)	

Abbreviations: IVIg= Intravenous immunoglobulin; TUH = Thammasat University hospital; BIH = Bangkok International hospital; GBS = Guillain-Barré syndrome; MG = Myasthenia Gravis; CIDP = chronic inflammatory demyelinating polyneuropathy; ALS = amyotrophic Lateral Sclerosis; MMN = multifocal motor neuropathy; MGUS= monoclonal gammopathy of unknown significance; NMOSD = Neuromyelitis Optica spectrum disorder; SNHL = Sensorineural hearing loss; HSV = Herpes simplex virus; NLEM= National list of essential medicine

Table 4: Mean GBS disability scale at admission and 6 months, mRC sum score at 7 days and good outcomes of treatment (GBS disability scale ≤ 3 at 6 months) between time of treatment.

	n	At admission	At 6 months	*p*
GBS disability scale (mean)		3.63 + 0.831	1.24 ± 1.648	0.000
IVIg use		mRC sum score Before treatment	mRC sum score At 7 days	
After disease onset ≤ 14 days	48	39.93 ± 15.209	47.36 ± 14.520	0.000
After disease onset > 14 days	10	39.60 ± 16.297	40.60 ± 18.500	0.634
IVIg use		GBS disability scale < 3 at 6 months	GBS disability scale ≥ 3 at 6 months	
After disease onset ≤ 14 days	45	37 (82.2%)	8 (17.8%)	0.261
After disease onset > 14 days	9	6 (66.7%)	3 (33.3%)	0.453

Abbreviations: IVIg=Intravenous immunoglobulin; MFS = Miller Fisher Syndrome; AMAN = Acute motor axonal neuropathy; AMSAN =Acute motor sensory axonal neuropathy; mRC = Medical Research Scale; mEGOS = Modified Erasmus GBS Outcome (mEGOS)

Table 5: Association between mEGOS score at admission and at 7 days after admission and good outcomes of treatment at 6 months measured by GBS disability scale.

	n	GBS disability scale < 3 at 6 months	GBS disability scale ≥ 3 at 6 months	p
At admission	n			0.075
mEGOS < 5	33	29 (87.9)	4 (12.1)	
mEGOS ≥ 5	18	12 (66.7)	6 (33.3)	
At 7 day after admission				0.010
mEGOS < 7	39	36 (92.3)	3 (7.7)	
mEGOS ≥ 7	12	5 (41.7)	7 (58.3)	

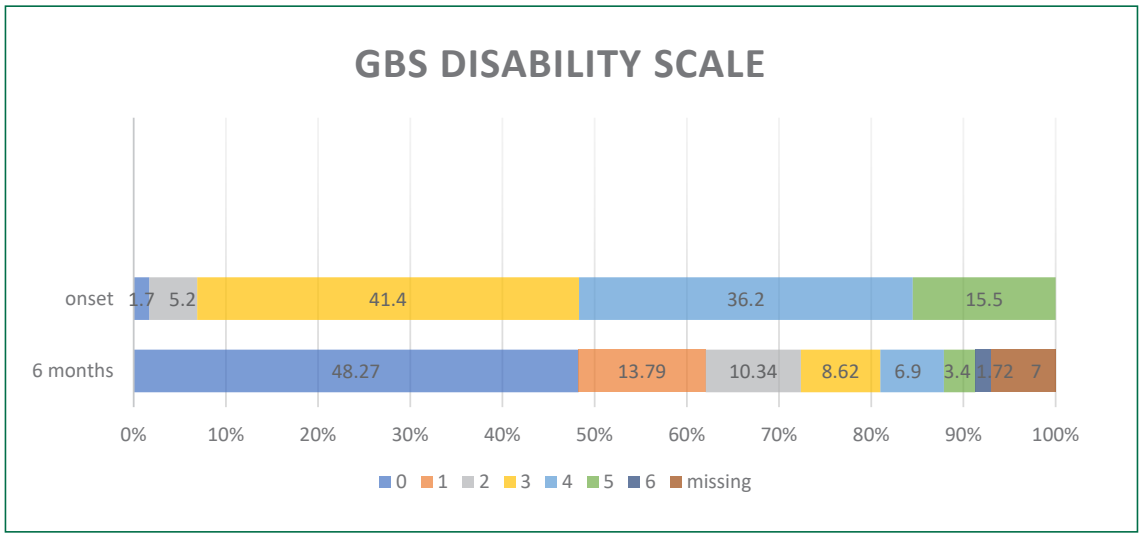

Figure 1: GBS disability scale at admission compared with 6 months.

MG

Twenty-seven patients received IVIg for suspected MG crisis. There was no significant difference between the two hospitals in baseline data, except respiratory failure, Acetylcholine receptor antibody status and precipitating causes. The major cause of precipitating causes was infection. All patients from TUH needed ventilator support. Three of them died due to ventilator acquired pneumonia and one TUH had an unresectable malignant thymoma. Two patients were misdiagnosed, one was congenital myasthenia syndrome and one did not have a definite diagnosis. Two patients were prescribed 0.5 g/kg of IVIg every two months as maintenance therapy for MG. Demographic data of patient and outcomes of treatment are shown in Table 6 and Table 7.

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Table 6: Demographic data of MG patients between two hospitals (TUH and BIH).

Indication	Total n = 114	TUH n = 28	BIH n = 86	*p*
Gender				
Male	10 (37)	5 (38.5)	5 (35.7)	1
Female	17 (63)	8 (61.5)	9 (64.3)	
Age (years)	54.52 ± 19.508	47.54 ± 18.791	61 ± 18.472	0.105
Thymoma				
Yes	7 (25.9)	6 (46.2)	1 (7.1)	0.033
No	20 (74.1)	7 (53.8)	13 (92.9)	
Clinical symptoms				
Respiratory failure	18 (66.7)	13 (100)	5 (35.7)	0.001
Ptosis and oculomotor disturbance	20 (74.1)	12 (92.3)	8 (57.1)	0.077
Cranial nerve palsy and bulbar weakness	7 (25.9)	3 (23.1)	4 (28.6)	1
Generalized weakness	21 (77.8)	10 (76.9)	11 (78.6)	1
Fluctuation of symptoms	13 (48.1)	8 (61.5)	5 (35.7)	0.257
MGC prior treatment	25.42 ± 9.807	28.77 ± 8.719	22.08 ±10.004	0.082
Diagnosis				
Repetitive nerve stimulation test				
Positive	22 (81.5)	11 (84.6)	11 (78.6)	0.617
Negative	5 (18.5)	2 (15.4)	3 (21.4)	
Acetylcholine receptor antibody				
Positive	18 (66.7)	12 (92.3)	6 (42.9)	0.011
Negative	9 (33.3)	1 (7.7)	8 (57.1)	
Precipitating cause				0.001
Infection	13 (48)	11 (84.6)	2 (14.3)	
Vaccine preventable	4	4	0	
Vaccine non-preventable	9	7	2	
Medical non-compliance	2 (7.4)	0	2 (14.3)	
Unknown cause	12 (44)	2 (15.4)	10 (71.4)	
IVIG dosage				0.153
0.4 g/kg	1 (3.7)	0	1 (7.1)	
0.5 g/kg	3 (11.1)	0	3 (21.4)	
1 g/kg	10 (37)	5 (38.5)	5 (35.7)	
2 g/kg	13 (48.1)	8 (61.5)	5 (35.7)	
Treatment outcomes				
Discharge status				
Survive	24 (88.9)	10 (76.9)	14 (100)	0.098
Death	3 (11.1)	3 (23.1)	0	
Length of ICU stay	3 ± 5.602	2.15 ± 4.776	3.79 ± 6.351	0.460
Length of respiratory support	9.22 ± 5.602	15.69 ± 32.755	3.21 ± 5.794	0.173
Length of hospital stay	15.15 ± 24.469	20.23 ± 33.892	10.43 ± 9.346	0.307
MGC scale after treatment 14 days	8.64 ± 7.650	3.4 ± 2.011	13 ± 7.920	0.001
NLEM				
Yes	20 (74.1)	12 (92.3)	8 (57.1)	0.077
No	7 (25.9)	1 (7.7)	6 (42.9)	
Cause of deviation				
Terminal illness	1 (14.28)	1 (100)	0	
Unknown definite diagnosis	1 (14.28)	0	1 (16.67)	
Congenital myasthenia syndrome	1 (14.28)	0	1 (16.67)	
Regular IVIG use	2 (28.57)	0	2 (33.33)	
New diagnosis and no current medication	2 (28.57)	0	2 (33.33)	
Length of respiratory support	9.22 ± 5.602	15.69 ± 32.755	3.21 ± 5.794	0.173

MGC MG composite MGC

Table 7: Outcome of treatment measured by MGC score before treatment and 14 days after treatment

	MGC score Prior Treatment	MGC score After Treatment	p
All patients	24.41 ± 9.148	8.64 ± 7.650	0.000
TUH	28.77 ± 8.719	3.40 ± 2.011	0.000
BIH	22.08 ±10.004	13.00 ± 7.920	0.009
IVIg dosage			
1g/kg (10)	20.60 ± 4.671	6.70 ± 6.516	0.001
2 g/kg (9)	28.11 ± 8.753	7.56 ± 5.961	0.001

CIDP

At BIH, seven patients were newly diagnosed CIDP. IVIg was used as first line therapy in 5 patients and second line in 2 patients. All of them used IVIg as maintenance therapy once a month. The baseline characteristics, clinical data, IVIg dosage and outcome of treatment are shown in Table 8. Five patients had improved INCAT disability score and five patients had improved mRC sum score at 6 weeks. All of them had favorable of treatment at 6 months. There were no patients recorded receiving IVIg for CIDP in TUH.

Transverse myelitis and NMOSD

Four patients form BIH were presented with transverse myelitis. One of them was diagnosed with idiopathic transverse myelitis and the others were diagnosed with NMOSD. All of them were treated with high dose steroid but their weakness did not improve. After that, they were prescribed IVIg 2 g/kg. Demographic, clinical data and treatment outcomes are shown in Table 9. Three patients had improvement at one year based on EDSS score and mRS scale.

Autoimmune encephalitis

Six patients were treated for autoimmune encephalitis. The diagnosis was acute disseminated encephalomyelitis[2], LGI1- receptor encephalitis[1], probable autoimmune encephalitis[2]. All of them received five days of intravenous methylprednisolone prior to IVIg 2 g/kg. Demographic data, treatment and outcome are summarized in Tables 10-11. Five patients had improvement of outcome measured by mRS at 1 year, seizure reduction > 50% and reduction of antiepileptic drugs. Baseline data, clinical data, IVIg dosage and outcome of treatment of patients in other neurological diseases are shown in Table 12.

Discussion

In Thailand IVIg is used in neurological and non-neurological disease such as primary immunodeficiency disease, Kawasaki disease, idiopathic thrombocytopenic purpura etc. Our data shows that the most common indication for IVIg is in neurological diseases, i.e. GBS, MG and CIDP. At TUH, IVIg was strictly used following NLEM indications due to reimbursement policy. However, at BIH, IVIg was used following NLEM indication or apart from NELM indication but the dose used was within standard guidelines. No major adverse effects were found in our cohort.

The difference of IVIg usage between TUH and BIH was clear in CIDP, autoimmune encephalitis and NMOSD. In general, first line treatment of CIDP includes corticosteroid, IVIg or plasmapheresis. IVIg used as first line treatment in newly diagnosed CIDP was only recorded at BIH, not at TUH. This is due to hospital policy on reimbursement. Therefore, TUH during the study period (2013-1019) used IVIg as subsequent treatment after failure of corticosteroid therapy. A pharmacoeconomic study in Thailand found that IVIg plus corticosteroid was cost effective as a second line therapy compared to immunosuppressants plus corticosteroids for steroid resistant CIDP patients. From previous study, the estimated cost of 12-week maintenance IVIg was 3,199 US dollars (body weight 50 kg) and the estimated cost of prednisolone plus azathioprine was 741 US dollars.[22] A similar study in Canada also found that IVIg was not perceived as cost-effective for first line treatment for CIDP, similar to study in Thailand.[22,23]

Due to the absence of IVIg indication in autoimmune encephalitis and NMOSD, the patient could not reimburse the cost of treatment. They then have to pay out of pocket and decide between the treatment options of IVIg and plasmapheresis. In TUH and public hospitals, the cost of plasmapheresis is lower than IVIg (In TUH, 219,230 THB for 7 cycles of plasmapheresis and 259,800 THB for IVIg estimated from bodyweight 50 kg), so TUH preferred plasmapheresis combined with high dose steroid rather than prescribing IVIg. Given the small number of cases, the treatment outcome cannot be reliably evaluated. Nevertheless, one paper from Thailand showed its efficacy.[24] IVIg now is being proposed to be included into the reimbursement list of NLEM.

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Table 8: Demographic data and treatment outcome of CIDP patients.

Case	Gender	Age (years)	Clinical data	Diagnosis	Disease duration (months)	Clinical status prior treatment			Prior treatment	IVIG dosage (g/kg)	Immunosuppressive drugs	Clinical status at 6 weeks			Outcomes of treatment at 6 months
						mRC	mRS	INCAT				mRC	mRS	INCAT	
1	F	20	Distal extremities weakness	CIDP	12	48	3	4	None	2	None	44	3	4	Improve
2	M	68	Quadriparesis	CIDP	24	54	2	3	None	1	None	54	2	2	Improve
3	M	65	Paraparesthesia	CIDP	2	58	1	1	None	2	None	60	1	1	Improve
4	M	52	Quadriparesis	POEM with plasmacytoma	3	46	4	5	None	2	Oral prednisolone	50	3	4	Improve
5	M	45	Quadriparesis	CIDP	12	42	4	7	Prednisolone, MMF	2	Prednisolone, MMF	49	4	6	Improve
6	F	86	Quadriparesis	CIIDP	3	42	4	8	None	2	None	48	3	6	Improve
7	F	50	Quadriparesis	CIDP with history AIDP	3	52	3	4	IVIG 2 g.kg	0.4	None	56	2	2	Improve

Table 9: Demographic data and treatment outcome of transverse myelitis and NMOSD patients.

Case	Gender	Age (years)	Clinical data	Diagnosis	Disease duration (months)	Clinical status prior treatment		Organ involvement	AQO-4 antibody	IVIG dosage (g/kg)	Treatment after onset	Plasma-pharesis	Immunosuppressive drugs	Clinical status next 1 year		Outcomes of treatment at 1 year
						EDSS	mRC							EDSS	mRC	
1	F	54	Fever, quadriparesis and bowl bladder involvement	Idiopathic transverse myelitis	2	7	37	Spinal cord at C2-C7, bilateral thalamus	Negative	2	6	No	None	4	52	Improve
2	F	42	Paraplegia and paraparesthesia	NMOSD	30	8	27	Spinal cord at C2-C3, C5-T2	Positive	2	37	No	None	5	48	Improve
3	F	22	Quadriparesis	NMOSD	7	8	21	Spinal cord lesion at C2-T1,	Positive	2	9	No	None	5	45	Improve
4	M	53	Paraplegia	NMOSD	30	8	36	Spinal cord lesion at T10-L3	Positive	2	37	Yes	Oral prednisolone	7	36	No improve

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Table 10: Demographic data and treatment of autoimmune encephalitis patients.

Case	Gender	Age (years)	Clinical symptoms	Disease duration (days)	Diagnosis	mRS at disease onset	EEG findings	Steroid	IVIG dosage (g/kg)	Treatment after disease onset (days)	Plasmapharesis	Immunotherapy
1	M	34	Aggression, behavior change and abnormal movement	33	Acute disseminated encephalomyelitis	4	Severe diffuse encephalopathy	Methylprednisolone 1 gm IV x 5 days	2	38	no	Dexamethasone 4 1x2 po pc
2	M	19	Fever and supra-refractory status epilepticus	3	Probable autoimmune encephalitis	5	Non-convulsive status epilepticus	Methylprednisolone 1 gm IV x 5 days	2	13	no	Prednisolone 5 6x2 po pc
3	M	74	Fever, alteration of consciousness and status epilepticus	22	Acute disseminated encephalomyelitis	5	BiPLED	Methylprednisolone 1 gm IV x 5 days	2	19	no	Prednisolone 5 6x2 po pc
4	F	50	Alteration of consciousness and behavior change Amnesia, behavior change	1	Neuropsychiatric systemic lupus erythematosus with immune thrombocytopenic purpura	5	Severe diffuse encephalopathy	Methylprednisolone 1 gm IV x 5 days	2	3	no	Dexamethasone 10 mg IV q 6 hr
5	M	41	and alteration of consciousness Abnormal movement,	24	Probable autoimmune encephalitis ,diagnosis primary CNS lymphoma	5	Moderate diffuse encephalopathy	Methylprednisolone 1 gm IV x 5 days	2	32	yes	Prednisolone 5 6x2 po pc
6	M	53	behavior change	365	Definite autoimmune encephalitis (LGI-1 encephalitis)	2	Continuous slow at bilateral temporal area	Methylprednisolone 1 gm IV x 5 days	2	367	no	Prednisolone 5 6x2 po pc, Azathiopine 50 2x1 po pc

Table 11: Outcome of treatment in autoimmune encephalitis patients.

Case	Length of ICU stay	Length of hospital stay	Length of endotracheal intubation	Seizure reduction > 50%	Reduction of antiepileptic drug	mRS before discharge	mRS at 12 months or last follow up	Outcomes
1	0	17	0	No clinical seizure		3	1	Improve
2	16	16	16	yes	yes	5	Referred to his country	Improve
3	10	41	8	yes	yes	3	3	Improve
4	9	17	3	No clinical seizure		3	1	Improve
5	27	48	21 followed by tracheostomy	No clinical seizure		6	6 1	Did not improve Improve
6	0	6	0	No clinical seizure		1		

Table 12: Demographic data and treatment outcomes of other diseases.

Case	Gender	Age (years)	Clinical data	Diagnosis	Disease duration (months)	Clinical status prior treatment		IVIG dosage (g/kg)	Immunosuppressive drug and other treatments.	Clinical status at 6 weeks		Outcomes of treatment
						mRC	mRS			mRC	mRS	
1	M	53	Quadriparesis	IgM MGUS	2	38	3	2	Oral prednisolone	44	3	No respond
2	M	66	Quadriparesis	ALS	4	40	3	2	No	36	4	No respond
3	F	23	Quadriparesis	MMN	5	40	3	2	No	Lost follow up		Lost follow up
4	M	46	Quadriparesis	ALS	6	38	4	2	Oral prednisolone, azathioprine	36	4	No respond
5	M	60	Asymmetrical weakness both arm and leg	Mononeuritis multiplex (P-ANCA)	1 weeks	50	3	2	Intravenous methylprednisolone, oral prednisolone, cyclophosphamide	48	3	No respond
6	F	49	Right ear pain and tinnitus	Sensorineural hearing loss	156	60	0	0.5	No	60	0	No respond
7	F	46	Right ear pain and tinnitus	Sensorineural hearing loss	1 weeks	60	0	0.5	No	60	0	No respond
8	F	53	Right arm pain and numbness	Postherpetic neuralgia	4	60	0	0.5	Gabapentin, amitriptyline	60	0	No respond
9	F	52	Left facial pain	Trigiminal neuralgia	12	60	0	0.5	Carbamazepine, pregabaline	60	0	No respond
10	F	43	Right arm numbness with history HSV radiculomyelitis	HSV radiculomyelitis	72	60	3	0.5	No	60	0	No respond
11	F	46	Proximal muscle weakness, dysphagia with history breast cancer on PEG feeding	Dermatomyositis with breast cancer	4	36	5	1 g/kg 2 dose	Prednisolone, MMF, Rituximab	36	5	No respond and terminate treatment

For GBS, the usage of IVIg in TUH is similar to BIH. Both hospitals preferred IVIg over plasmapheresis because of its established efficacy, safety and convenience. A retrospective study from the US showed that plasmapheresis prolonged hospital stays, leading to greater hospitalization costs and increased in-hospital death.[25] In our opinion, IVIg is a suitable treatment for GBS in Thailand. Our study shows that the IVIg total 2 g/kg improves recovery of weakness and reduces long-term morbidity at 6 months. Our previous study and randomized controlled trial have shown efficacy of IVIg within 2 weeks after onset in hastening recovery.[26] The mEGOS score can be applied as a prognostic model for poor outcome at 6 months. Higher mEGOS score predicts poorer outcomes and may need additional management during the acute period. From the non-randomised ISID study, second IVIg course in GBS with poor prognosis from higher mEGOS score did not show further benefit on functional outcomes.[27] Further clinical trials are needed to evaluate other treatment options in poor prognosis patients. From our study, the GBS subtype, indication of IVIg and treatment outcomes are similar to other studies worldwide.

IVIg usage in acute exacerbation of MG in TUH strictly followed NLEM indication, patient must have severe weakness, bulbar weakness and impending crisis, which is different from the criteria at BIH. Two patients from BIH used IVIg as maintenance therapy. This practice is uncommon in Thailand and costly. Seven studies showed that maintenance IVIG therapy may reduce symptoms and reduced dosage of steroid and immunosuppressive drugs, but it may be ineffective in inducing remission or reducing disease activity.[28-30] Maintenance IVIg may be a useful therapeutic modality in very refractory MG is and in patients who cannot tolerate steroid or immunosuppressive medications.

There is controversial evidence of IVIg usage in acute attack of transverse myelitis and NMOSD. First line treatment is high dose steroid and second line treatment is plasmapheresis.[31-34] In our study four patients were treated with IVIg after failure of high dose steroid and their weakness slowly improved. None of them had relapsing disease and three of them had improved in EDSS after 1 year. From our data, IVIg may have benefits in acute treatment of NMOSD. Another study showed IVIg alone was less beneficial than high dose steroid but early IVIg followed by high dose steroid in severe patient (EDSS > 6) was superior to high dose steroid. In patients whose condition failed to improve with high dose steroid, adding IVIg did not improve the outcomes.[35] So early initiation of IVIg combined with high dose steroid in severe NMOSD patient may be beneficial but a long term randomized controlled trial is needed to establish the role of IVIg in NMOSD.

The use of immunotherapy in autoimmune encephalitis is quite common but the rationale relies mostly based on retrospective cohort and expert opinions. First line therapy consists of corticosteroids plus IVIg or plasma exchange.[36,37] There is no strong evidence of a difference between

plasmapheresis and IVIg. In our cohort, administration of IVIg was associated with seizure reduction > 50%, reduction of antiepileptic drugs and improve functional outcomes measured by mRS score in LGI-1 encephalitis patient and ADEM. IVIg can be considered the therapeutic option in LGI-1 encephalitis. Similar to previous data, ADEM and encephalitis associated antibodies against neuronal surface target included LGI-1 have better prognosis than those associated with intracellular antibodies.[37, 38] IVIg treatment in patients with suspected probable autoimmune encephalitis may be beneficial in seizure reduction, but their prognosis was still poor. Larger randomized controlled trial of IVIg in ADEM and encephalitis associated antibodies against neuronal surface antibody is eagerly awaited.

The misuse of IVIg in our cohort include primary CNS lymphoma, congenital myasthenic syndrome, ALS, monoclonal gammopathy,[39] sensorineural hearing loss, trigeminal neuralgia, postherpetic neuralgia and HSV radiculomyelitis. Due to the severity of disease, patient with primary CNS lymphoma and congenital myasthenic syndrome were prescribed IVIg before getting the diagnosis. Patients in this group did not get the benefit from IVIg. A small prospective trial showed IVIg may be effective in reducing pain in patients suffering from chronic neuropathic pain[40,41] but the cost of treatment is a concern.

This study had several limitations. Firstly, this is retrospective study and all review data depended on medical records. Secondly, this study reviewed usage of IVIg in neurological disease, which are quite varied and some had no standardized outcome parameters. Lastly, the number of patients in TUH and some disease such as dermatomyositis and MMN was lower than expected so this study could not show the clear efficacy of IVIg in these uncommon diseases and would not truly represent university hospitals in Thailand.

Conclusion

In conclusion, IVIg usage in TUH is similar to BIH in GBS and MG and provided similarly good outcomes. BIH used IVIg as first line treatment in CIDP, compared to second line treatment after failure of corticosteroid in TUH. IVIg may provide benefits in autoimmune encephalitis especially ADEM and encephalitis associated antibodies against neuronal surface target. Early combination IVIg with and high dose steroid may have benefits in severe degree NMOSD.

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