Intravenous immunoglobulin response in treatment-naïve chronic inflammatory demyelinating polyradiculoneuropathy

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ABSTRACT

Objective: There is no consensus which treatment should be used preferentially in individual patients with chronic inflammatory demyelinating polyneuropathy (CIDP). Patients unlikely to respond to IV immunoglobulin (IVIg) could be prescribed corticosteroids first to avoid high cost and a delayed treatment response. We investigated which factors determined a response to IVIg.

Methods: Treatment-naïve patients with CIDP initially treated with at least one full course of IVIg (2 g/kg) at one of two neuromuscular disease centers were included. Patients fulfilled the European Federation of Neurological Societies/Peripheral Nerve Society clinical criteria for CIDP. Significant improvement following IVIg was defined as an improvement (≥1 grade) on the modified Rankin scale. Difference in weakness between arms and legs was defined as ≥ 2 grades on the Medical Research Council scale between ankle dorsiflexion and wrist extension. Clinical predictors with a p-value <0.15 in univariate analysis were analysed in multivariate logistic regression.

Results: Of a total of 281 patients, 214 patients (76%) improved. In univariate analysis, the presence of pain, other autoimmune disease, difference in weakness between arms and legs, and a myelin-associated glycoprotein negative IgM monoclonal gammopathy of undetermined significance were associated with no response to IVIg. In multivariate analysis no pain ($p = 0.018$) and no difference in weakness between arms and legs ($p = 0.048$) were independently associated with IVIg response. Of IVIg non-responders, 66% improved with plasma exchange and 58% with corticosteroids.

Conclusion: IVIg is a very effective first-line treatment. Patients with CIDP presenting with pain or a difference in weakness between arms and legs are less likely to respond to IVIg.

INTRODUCTION

In randomised controlled trials, intravenous immunoglobulin (IVIg), plasma exchange (PE) and corticosteroids have been shown to be beneficial in the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP).[1-7] The long-term benefits and safety of IVIg in CIDP has been demonstrated in a large randomised placebo-controlled trial in CIDP.[4] Some patients improve more after one of the effective treatments than after another and some can even fail to show a response to one or more of these proven effective treatments.[8-11]

There is no consensus on which is the best treatment for individual cases of CIDP.[12] In order to give the most appropriate treatment in the earliest phase of the disease it would be helpful to identify patients who are more likely to respond to one particular treatment.[8,10] Corticosteroids and IVIg differ in terms of cost, speed of action and adverse events.[13,14] Although expensive, IVIg is often considered a treatment of first choice because of its rapid onset of action compared to the usually slower response to steroids, and because it has a better long-term adverse event profile.[9,15-18] Sometimes only one course of IVIg is sufficient to induce a sustained remission.[12] Corticosteroids are usually prescribed for a lengthy period and require a slow tapering over several months, and thus may be accompanied by serious side effects.[15,19] During that extended period it is likely that some patients may still be treated with corticosteroids although they may already have reached remission.[17] For a yet unknown reason, not all patients improve after IVIg and a delay in starting effective treatment could result in secondary axonal damage that is potentially resistant to treatment.[9] To avoid high cost and to minimise the probability of secondary axonal damage due to the prescription of an ineffective treatment, standard dose steroids or high-dose pulse corticosteroids could be given as a first-line treatment to patients unlikely to respond to IVIg if it can be proven that they are better off with corticosteroids.[19-20] PE is generally considered after the patients fail to respond to IVIg and steroid treatment. PE is relatively inconvenient as special equipment is needed, good venous access is required and there is a risk of adverse events. We have investigated which clinical as well as neurophysiological factors might be associated with a good response to IVIg in a previous single-centre cohort of 52 patients with CIDP.[1]

The aim of this study was to investigate in a larger group of treatment-naïve patients with CIDP which clinical factors are associated with a good response to IVIg, to be able to optimise and personalise treatment at onset.

METHODS

Patients

In this retrospective study we combined data from medical records of patients with CIDP from two large university hospitals (Erasmus MC, University Medical Centre Rotterdam, the Netherlands and London Health Sciences Centre London Ontario, Canada). Patients were diagnosed as CIDP and followed over time by a consultant neurologist (AFH, PAvD, MV, SLV) experienced in neuromuscular diseases, and treated with IVIg between 1980 and 2011 (N = 152 Erasmus MC; N = 129 London Health Sciences Centre). All patients fulfilled the European Federation of Neurological Societies/Peripheral Nerve Society clinical diagnostic criteria for typical or atypical (still considered CIDP but with different features) CIDP.[15] Twenty-five of these patients have been described previously.[1] Not all these patients were included in the current study mainly because they were not all treatment-naïve or they were diagnosed differently over time. Patients with recurrent Guillain-Barré syndrome (GBS) or GBS patients with treatment-related fluctuations were excluded.[21] Patients with multifocal motor neuropathy (MMN) as well as patients with any other chronic acquired or hereditary neuropathy were excluded. Patients with an IgG or IgM monoclonal gammopathy of undetermined significance (MGUS) were only included when they had a clinical course fully consistent with CIDP. Patients with an IgM MGUS who had antibodies against myelin-associated glycoprotein were excluded.

Treatment and response

All patients were treated with IVIg as a first treatment modality and completed at least one full course of IVIg (2 g/kg over 2-5 days). Before IVIg was available some of the patients initially received fresh frozen plasma (FFP).[1,22] Because these patients (N = 15) were treated with IVIg thereafter and showed the same response to FFP as to IVIg it was unlikely that this would have any effect on the results, therefore, they were included in the current study. The 281 patients were followed with a mean duration of 5.2 years (median 3.8 years, range 20 days-28 years).

Clinically important improvement following treatment was defined as an improvement (decrease) of ≥ 1 grade on the modified Rankin scale (range 0-5).[23] When it was unclear whether a patient responded significantly, a second course of IVIg was given. When patients required maintenance IVIg treatment, regular attempts to reduce the dosage were performed to check whether patients were in remission or were still IVIg dependent.

To investigate the response rate to corticosteroids or PE in patients who failed to respond to IVIg, we only analysed data from patients treated with sufficiently large dosages of steroids as monotherapy (e.g. prednisolone ≥ 60 grams a day for at least 6 weeks) or patients who received at least five PE sessions as monotherapy.

Definitions of patient characteristics

Subacute CIDP was defined as an onset phase of 4-8 weeks. All patients with a subacute onset included in this study subsequently had a chronic progressive or relapsing course requiring long-term (IVIg) treatment. Asymmetrical weakness was defined as a difference ≥ 2 grades on the Medical Research Council (MRC) scale in at least one muscle pair (shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, ankle dorsiflexion). A difference in weakness between arms and legs was defined as a difference of ≥ 2 grades on the MRC scale between ankle dorsiflexion and wrist extension. The level of the modified Rankin scale at nadir was defined as the worst score prior to or after start of treatment. Pure motor CIDP was defined as CIDP without sensory signs and abnormalities in sensory nerve conduction studies. Pure sensory CIDP was defined as pure sensory symptoms and signs at presentation, nerve conduction studies in these patients, however, could show some minor abnormalities in motor nerve studies and muscle weakness could appear subsequently during follow-up. A clinical remission was defined as a modified Rankin score 0-1 after discontinuation of treatment. Children were defined as <18 years old when IVIg was started. Medical records and letters were reviewed for the occurrence of (other) autoimmune disorders. Since patients were treated by the same consultant neurologist (AFH, PAvD, MV, SLV) from one of the two university hospitals, we could screen the medical records for the occurrence of pain and whether patients were treated with analgaesics. When the presence of pain was not reported and when analgaesics were not used we assumed that pain was not present. We did not analyse EMG findings because these examinations were not always performed in a standardised fashion in this two-centre study.[12, 24-25]

Statistical analysis

The literature was screened for important known factors that might be associated with a response to IVIg. These factors that were present in our data as well as other variables that in our opinion seemed relevant to IVIg response were analysed. To compare relative differences between IVIg responders and non-responders χ^2 test, Fisher's exact test, or Mann-Whitney *U* test were used. For the categorical variables polyneuropathy type and weakness distribution the χ^2 test for trend was used, which gives the overall p value. Predictors that had a p value of < 0.15 in univariate analysis were selected to be analysed in multivariate logistic regression. This level of 0.15 was chosen to improve the power to identify important predictors.[26] Multivariate logistic regression was used to identify which factors were associated with a good response to IVIg. Analysis was performed using SPSS V.20.0. A two-sided p value < 0.05 was regarded significant. The Hosmer-Lemeshow test was used to check for goodness-of-fit.

RESULTS

Patient characteristics

A total of 281 treatment-naïve patients with CIDP initially treated with at least one full course of IVIg (2 g/kg) were included. Main clinical characteristics of these patients are shown in Table 1. Thirty-five patients (13%) were known to have a concurrent autoimmune or immune-mediated disorder (Table 2).

Table 1. Clinical characteristics of IVIg responders and non-responders

		Responsive to IVIg		
	Total (n = 281)	Yes (n = 214)	No (n = 67)	**p Value**
Patient characteristics				
Male	179 (64%)	133 (62%)	46 (69%)	0.33
Children	13 (5%)	10 (5%)	3 (5%)	0.95
Progression of weakness*	267 (95%)	205 (96%)	62 (93%)	0.33
Other autoimmune disease^	35 (13%)	22 (10%)	13 (19%)	**0.048**
Pain^	77 (27%)	50 (23%)	27 (40%)	**0.007**
Subacute onset	29 (10%)	25 (12%)	4 (6%)	0.18
Polyneuropathy type				
Pure motor	37 (13%)	28 (13%)	9 (13%)	
Pure sensory	29 (10%)	22 (10%)	7 (10%)	
Sensory-motor	215 (77%)	164 (77%)	51 (76%)	0.93[#]
Areflexia legs	235 (84%)	175 (83%)	66 (90%)	0.17
Areflexia arms	209 (75%)	155 (73%)	54 (81%)	0.22
Weakness symmetrical	251 (94%)	190 (94%)	61 (94%)	0.94
Weakness distribution				
Legs = arms	170 (62%)	140 (68%)	30 (46%)	
Legs > arms	89 (33%)	56 (27%)	33 (50%)	**0.002**[#]
Legs < arms	14 (5%)	11 (5%)	3 (5%)	
IVIg treatment				
Time symptoms to first treatment, mo	4 (1-11)	3 (1-10)	4 (2-13)	0.75
Age start treatment, y	52 (39-62)	49 (39-61)	53 (42-65)	0.66
Laboratory				
IgG MGUS	14 (5%)	13 (7%)	1 (2%)	0.131
IgM MGUS (anti-MAG negative)	7 (3%)	3 (2%)	4 (6%)	**0.036**

Data are numbers (%) and compared using $\chi 2$ test, Fisher's exact test or $\chi 2$ test for trend, or median (IQR) and compared using Mann-Whitney *U* test.
* In the months prior to IVIg start.
^ These variables were assumed to be absent when they were not reported in medical files.
[#] Overall p-value.
IVIg = intravenous immunoglobulin;
MGUS = monoclonal gammopathy of undetermined significance;
MAG = myelin-associated glycoprotein.

Table 2. Presence of other autoimmune disease (N = 35)

Autoimmune disease	Number of patients
Rheumatoid arthritis	6
Thyroid gland disorder	5
Insulin-dependent diabetes mellitus (IDDM)	5
Inflammatory bowel disease	3
Interstitial nephritis	4
Systemic lupus erythematosus	2
Sjögren's syndrome	1
Systemic sclerosis	1
Psoriasis	1
Asthma	1
Immune thrombocytopenic purpura	1
Crohn's disease + IDDM + thyroid gland disorder	1
Multiple sclerosis + thyroid gland disorder	1
IDDM + thyroid gland disorder	1
Ulcerative colitis + thyroid gland disorder	1
Bechterew + psoriasis	1

Treatment response

The response rate to IVIg was 76% (214/281). The response to IVIg was not significantly different in children than in adults (76% vs. 77%, p = 0.95). Most patients who failed to improve with IVIg received subsequent treatment: 66% improved with PE and 58% with corticosteroids (Figure 1). Of the IVIg non-responders who were treated with at least one other treatment modality, 79% responded either after PE, corticosteroids or both. Only three patients did not respond to any of the three treatments. In 11 out of 37 pure motor CIDP patients, steroids were given with a response rate of 46% (5/11). From 86 treatment-naïve patients who were IVIg responsive and reached a documented clinical remission, 14 (16%) needed only one IVIg course.

Clinical characteristics associated with IVIg response

The age of the patients when IVIg was started, or the time from symptom onset to IVIg start, were not associated with treatment response (Table 1). Furthermore, the presence of a pure motor or sensory CIDP subtype was also unrelated to the response to IVIg. In univariate analysis no difference in weakness between arms and legs, no other autoimmune disease, no MGUS and the absence of pain were all positively associated with IVIg response. In multivariate analysis, no difference in weakness between arms and legs, and the absence of pain were both independently associated with IVIg response (Table 3). In multivariate analysis, the presence of another autoimmune disease or MGUS were not statistically significant associated with IVIg response when adjusted for the other

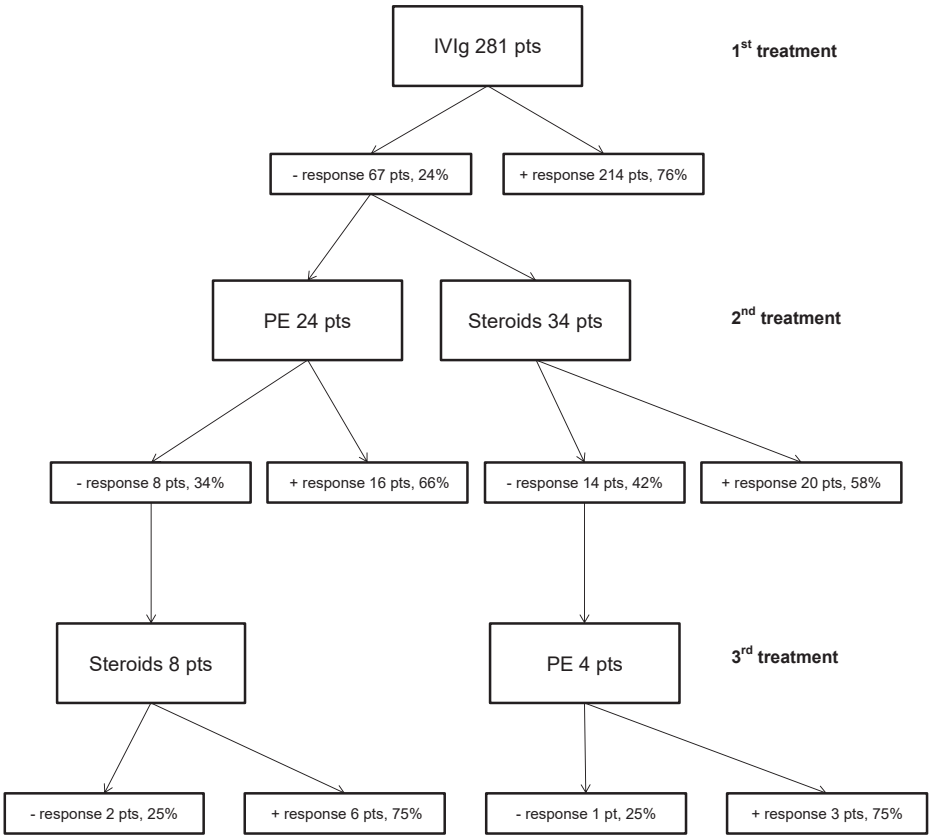

Figure 1. Treatment response in chronic inflammatory demyelinating polyradiculoneuropathy patients initially treated with intravenous immunoglobulin

variables. This model fitted the data well based on the Hosmer-Lemeshow statistic (p = 0.68). The presence of pain or a difference in weakness between arms and legs were not statistically significant associated with a treatment response to corticosteroids. An overview of factors that have been reported to be associated with a response to IVIg in CIDP in the literature is given in Table 4.

Adverse events

In 10 patients IVIg was discontinued due to adverse events. Although these were reasons to stop treatment, most were relatively minor, such as headache. Three of these patients had severe adverse events; one developed a Stevens-Johnson syndrome and two acquired haemolytic anaemia. None developed severe life-threatening adverse events such as an anaphylactic shock.

Table 3. Multivariate logistic regression of a good response to IVIg (N = 256)

	OR	95% CI	p Value
Pain			
No (ref.)	1.0		**0.018**
Yes	0.46	0.24 to 0.88	
Weakness distribution			
Arms = legs (ref.)	1.0		**0.048**[#]
Legs > arms	0.46	0.24 to 0.85	
Legs < arms	0.72	0.18 to 2.93	
Other autoimmune disease			
No (ref.)	1.0		0.10
Yes	0.50	0.23 to 1.13	
IgG MGUS			
No (ref.)	1.0		0.22
Yes	3.73	0.46 to 30.09	
IgM MGUS (anti-MAG negative)			
No (ref.)	1.0		0.06
Yes	0.21	0.04 to 1.04	

[#] Overall p value.

IVIg = intravenous immunoglobulin; MGUS = monoclonal gammopathy of undetermined significance.; MAG = myelin-associated glycoprotein.

Table 4. Factors associated with a response to IVIg in CIDP: a review of the literature

Author	Year	Number of patients	Number of treatment-naïve patients	Response rate to IVIg (%)	Associated with a good response to IVIg
van Doorn, et al. [1]	1991	52	not stated	62	Disease duration < 1 y Progression of weakness Absence of discrepancy between weakness of arms and legs Areflexia arms Slowed NCV of the motor median nerve
Choudhary, et al. [11]	1995	22	not stated	64	Female gender
Hahn, et al.[2]	1996	30	not stated	63	Acute relapse Disease duration < 1 y
Iijima, et al. [9]	2005	312	283	64	Female gender Shorter disease duration Fast progression of symptoms No axonal dysfunction
Tackenberg, et al. [18]	2007	76	76	82	Monophasic or relapsing-remitting form > twofold CSF protein increase
Iijima, et al. [42]	2009	100	100	72	TAG-1 gene polymorphism
Querol, et al. [43]	2014	53	not stated	74	No anti-NF155 antibodies

CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CSF = cerebrospinal fluid; IVIg = intravenous immunoglobulin; NCV = nerve conduction velocity; TAG-1 = transient axonal glycoprotein-1.

DISCUSSION

The high response rate to IVIg of 76% in our large cohort was similar to what has been reported before.[3,27-28] We used the modified Rankin scale to assess treatment response. This scale is easy to use and the cut-off point of ≥ 1 point has often been used for clinically relevant improvement in CIDP.[9-11,18,24,29] A disadvantage of this scale is, however, that it is probably too insensitive to show small but clinically meaningful functional improvements. Nonetheless, the percentage of patients who improved is still high and exceeds the improvement rate found in the largest RCT conducted in patients with CIDP.[4] The Peripheral Neuropathy outcome measures Standardisation (PeriNomS) study recently investigated which assessment scale is the most appropriate to use in future studies in inflammatory neuropathies.[30] Because we were mainly interested in large clinical meaningful differences in this retrospective study, we still consider that using the modified Rankin scale gives relevant information.

Clinical characteristics associated with IVIg responsiveness have been investigated in a larger group (N = 312) of IVIg treated patients with CIDP with a 64% response-rate.[9] However, only 283 of these patients were treatment-naïve (a similar number as our cohort), which may explain the somewhat lower response-rate.[9] Our current study showed that the absence of a discrepancy in upper and lower limb weakness is associated with IVIg responsiveness, which has been found previously in a small cohort of patients.[1] Pain has been reported to be prominent in 42% of CIDP patients, but has not been described as a risk factor for IVIg non-responsiveness before and should receive more attention in future studies.[29]

Thirteen per cent of the patients in our study were known to have a concurrent autoimmune disorder in addition to CIDP, a similar percentage has recently been reported in the literature in patients with MMN and in a survey on GBS and CIDP.[31,32] The overall prevalence of autoimmune disorders reported in the general population is 5%, suggesting that patients with CIDP have an increased risk of autoimmune disease and CIDP might be the result of an aberrant immune response.[31]

A higher response rate in children compared to adults, as has been suggested previously, was not found in our cohort.[33] Furthermore, age, sex and disease duration were not associated with IVIg responsiveness in our cohort.[1,9,11] Axonal dysfunction of peripheral nerves has been reported to be associated with a failure of IVIg response.[9] Whether nerve conduction studies are useful in the prediction of treatment response in CIDP remains unclear.[27,34-35]

In a recent study of 86 non-treatment-naïve patients with CIDP treated with IVIg, the only variable that was associated with reaching remission (asymptomatic without treatment) at long term was a better response during the first 6 months.[36] Unfortunately,

some patients in this study had been treated simultaneously with other immunosuppressive agents besides IVIg.[36]

Our study confirms that the (long term) adverse events of IVIg are minor and rarely a reason to discontinue treatment.[9,37] A recent trial over a treatment period of 6 months found that IVIg treatment was less frequently discontinued than intravenous methylprednisolone for reasons such as inefficacy, adverse events or intolerance.[20]

Our study indicates a higher response rate to steroids or PE prescribed as a second or even third treatment modality in patients unresponsive to IVIg than reported previously.[29] Therefore, treatment with corticosteroids or PE should be offered to patients with CIDP who do not respond satisfactorily to IVIg, knowing that there is still a good chance of improvement even with a third treatment modality.[15] Why some patients only respond to a particular treatment remains unknown and requires further investigation. Although 15% of patients with CIDP are reported to be unresponsive to all three treatment modalities, we could only identify three patients (1%) who were unresponsive to all three treatments in our study.[15] It has been reported that patients with CIDP who were unresponsive to steroid treatment often appeared to have been given an alternate diagnosis during follow-up.[38] Clinical data from the three patients in our cohort that were unresponsive to all three treatments were reviewed thoroughly in order to check whether we could find any evidence for an alternative diagnosis during the long-term follow-up. However, no diagnosis other than CIDP could be established. All had clinical features of CIDP and a raised CSF protein level, and either clear demyelinating abnormalities on EMG, sural nerve biopsy findings compatible with CIDP, or a spontaneous remission during follow-up that strongly indicates CIDP.

We investigated a large group of patients with CIDP who were treated with IVIg as a first treatment modality and were followed for a long period of time. It is possible that some patients with CIDP who were thought to have had a therapeutically induced remission had, in fact, a spontaneous remission, making it more difficult to judge treatment efficacy and to identify predictors associated with an IVIg response. Therefore, a large patient cohort, such as ours, is needed to identify important variables associated with treatment effect.[28,39] An important limitation of this study is its retrospective and open nature. Thereby, some items were not assessed systematically, such as the presence or absence of other autoimmune diseases or pain, and this could have lowered our chance of finding factors that are associated with a treatment response. A major limitation is the fact that the presence, severity and type of pain was not investigated in a standardised manner using existing scales. Sixteen per cent of our patients needed only one IVIg course to reach a clinical remission which is in line with the 15-30% reported in the literature.[15] Although no significant difference in remission rate was found in patients with CIDP treated with pulsed high-dose dexamethasone compared to prednisolone, intravenous methylprednisolone seemed to induce more long-term remissions than

IVIg.[19-20] Most of the IVIg non-responders from our cohort received more than one IVIg course. A study suggested that at least two IVIg courses over a period of 6 weeks may sometimes be required to identify an initial improvement.[39] Many patients from that cohort were different from ours as there was often a long delay between onset of symptoms and initiation of IVIg treatment, all patients received a second IVIg dosage after 3 weeks, and many already had fixed axonal deficits.[39] In our cohort, the diagnosis of CIDP was always established by a senior neurologist experienced in neuromuscular diseases possibly explaining the shorter treatment delay and the higher response rate to IVIg.[39] Since we already observed a relatively high treatment response it is unlikely that we missed a substantial number of patients who would have only responded after two or more IVIg courses. Recent data suggest considering an even longer treatment period with IVIg of more than 6 weeks before declaring a patient non-responsive.[40] Yet if one observes only a limited improvement with IVIg, one needs to explore the possibility of fixed neurological deficits caused by axonal degeneration as these in general do not improve with any treatment.

The ability to predict which patients are more likely to respond to IVIg will help physicians to choose the optimal initial treatment. This may prevent unnecessary delay of effective therapy, reduce cost and limit or avoid side effects. Early optimal and personalised treatment is not only needed to improve disability but is important to prevent permanent disability from on-going demyelination and secondary axonal loss.[39,41] As we showed, IVIg is a very effective treatment for CIDP and the short-term and long-term side effects are generally minor; but it is expensive and unfortunately most patients need long-term IVIg treatment. For patients with CIDP who do not suffer from pain or show a clear difference in weakness between arms and legs, IVIg is a good first treatment choice given its efficacy, fast speed of action and low side effect profile. By contrast, patients with CIDP with prominent pain or a clear difference in weakness between arms and legs are less likely to respond to IVIg. In view of the high cost of IVIg, to prevent unnecessary delay in improvement and because high-dose pulse steroid treatment might induce remission more often,[20] it should be further investigated whether these patients are better off being initially treated with corticosteroids.

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