

Original Research

Dramatic clinical response to ultra-high dose IVIg in otherwise treatment resistant inflammatory neuropathies

Mahima Kapoor^{*}, Mary M Reilly^{*,†}, Hadi Manji[†], Michael P Lunn^{†,‡}, Aisling S Carr[†]

^{*} MRC Centre for Neuromuscular Diseases, Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, Queen Square, London WC1N 3BG, UK.

[†] National Hospital of Neurology and Neurosurgery (NHNN), Queen Square, London WC1N 3BG, UK

[‡] Department of Neuroimmunology, UCL Queen Square Institute of Neurology, Queen Square, London WC1N 3BG, UK

Running Title: High dose IVIg in inflammatory neuropathies

Corresponding author:

Dr Aisling Carr

Consultant Neurologist

aisling.carr@nhs.net

Tel. +44 203 108 7524, Fax. +44 203 448 3633

Title character count= 89

Word count for abstract= 238

Word count for text= 3551

Figures= 2

Tables= 2

References= 45

Abstract

Background: Intravenous immunoglobulin (IVIg) has short and long-term efficacy in both chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy with conduction block (MMNCB). There is potential for under and over-treatment if trial regimens are strictly adhered to in clinical practice where titrating dose to clinical response is recommended.

Methods: We report the response to high-dose IVIg (>2g/kg/6weeks) in a subgroup of patients with definite CIDP or MMNCB who were unresponsive to 'usual' dosing. IVIg frequency and dosing was determined for each individual by subjective and objective outcome measures for impairment, grip strength, and activity and participation.

Results: Six patients (three with CIDP, three with MMN) were included. Two patients (one CIDP and one MMNCB) returned to full-time work on fractionated IVIg doses of 5g/kg/month and 9g/kg/month. Patient three (CIDP) failed numerous other immunosuppressants but responded to short-term fractionated 4g/kg/month of IVIg. Patient four has severe, refractory, childhood-onset CIDP, remains stable but dependent currently on 6.9g/kg/month of IVIg. Patients five and six, both with MMNCB, required short term 4.5-5g/kg/month to recover significant bilateral hand strength. No IVIg-related adverse events occurred in any individual.

Conclusion: These six cases demonstrate the safety and effectiveness of a treatment approach that includes individualised but evidence-based clinical assessment and, when necessary, high-doses of IVIg to restore patients' strength and ability to participate in activities of daily activities. Careful patient selection is important.

Keywords= inflammatory neuropathy, intravenous immunoglobulin, therapeutic dosing, outcome measure

Introduction

The chronic inflammatory neuropathies represent a clinically heterogeneous group of rare and disabling but treatable diseases. Regular infusions of intravenous immunoglobulin (IVIg) result in short and long term improvement in function and reduction in disability in both CIDP and multifocal motor neuropathy with conduction block (MMNCB) (1). The accepted dosing regimen for IVIg initiation (2g/kg over 3-5 days) originates from a 35-year old approach in children with idiopathic thrombocytopenic purpura (ITP) (2). This has been the standard starting dose in inflammatory neuropathy clinical trials followed by a lower maintenance regimen of 1g/kg/3 weeks (ICE, equivalent in PATH) (1,3–6). Retrospective analysis of maintenance IVIg in CIDP in real life clinical practice reveals marked variability in dose to weight ratios, with no correlation between optimal dosing regimen and current body weight or to level of initial disability reflecting the limited understanding of the mechanism of action, pharmacodynamics and pharmacokinetics of IVIg in this setting (7). Nevertheless, IVIg titration lead by close clinical outcome monitoring is recommended and allows most patients to tailor dose and frequency to less than 2g/kg every 6 weeks (8,9). However, a consistent minority relapse on lower doses (less than 1g/kg/3 weeks) (6,10). Measures such as fractionating the equivalent monthly dose and increasing infusion frequency can result in improvement in strength for some, but not all, patients (11). Therefore, strict adherence to dosing regimens used in the trial setting will result in inadequate treatment of a proportion of patients. Although generally well tolerated IVIg-related serious adverse events can occur, so caution is required when prescribing at doses outside the recommended range (12).

We present a series of patients with definite CIDP or MMNCB according to EFNS/PNS criteria, without nodal or paranodal antibodies, who were unresponsive to standard maintenance IVIg dosing: 0.4–1.2 g/kg, 2-6 weekly but in whom significant clinical and

electrophysiological recovery occurred with higher doses of IVIg which could then be relaxed to more standard doses later. Safety and tolerability of these regimens are described (13–16).

Methods

Patients with a severe and disabling disease course, refractory to IVIg at doses less than or equal to 2g/kg/6 weeks plus/ minus additional or alternative immunomodulatory and immunosuppressive treatments were identified from the inflammatory neuropathy cohort, Centre for Neuromuscular Diseases, National Hospital of Neurology and Neurosurgery, London. Case definition, clinical and demographic characteristics, IVIg regimen (g per infusion, frequency of infusion in weeks and dose in g/kg/month), clinical response (Medical Research Council sum score (MRC-SS (maximum 70)) and disease-specific Rasch-built Overall Disability Scale (RODS score) and pre- and mid-cycle serum IgG concentration were collected by retrospective case note review (17,18). These data are collected in routine clinical practice in our centre. Consent from patients to publish has been obtained. Optimal response was a collaborative decision between physician and patient based on achievement of adequate, stable and sufficient treatment impact. **Adequate** and **stable** response was defined as lack of peri-dose fluctuation and improved and maintained subjective and objective outcome measures. **Sufficient** response depended on the level of participation required by the individual in life situations, particularly occupation and pre-neuropathy level of fitness.

We calculated median pre-dose (trough) IgG levels and change in IgG levels (pre-dose and immediately post-dose) after at least two cycles during sub-optimal versus optimised IVIg treatment regimens. There is some evidence to suggest serum IgG concentrations is an individualised, surrogate marker of treatment adequacy (Table 2).

Statistical analysis was performed using the statistical package GraphPad Prism version 8.0.0

for Mac, GraphPad Software, La Jolla California USA, www.graphpad.com. In all tests, 2-tailed P values <.05 were considered significant. Consent to publish has been obtained from the patients.

Results

Six patients were identified from our cohort, 3 with definite CIDP and 3 with definite MMNCB as per ENFS diagnostic criteria. There were 4 males and 3 females, age of onset ranged from 8-47 years, symptoms developed acutely in 2 (<6 weeks to nadir with subsequent relapsing-remitting course) and the rest had a chronic course. Additional or alternative immunomodulatory or immunosuppressant medications in these patients included mycophenolate mofetil, IV and/or oral corticosteroids, IV cyclophosphamide, rituximab, azathioprine, beta-interferon, methotrexate, cyclosporine, tacrolimus, alemtuzumab, fingolimod and one patient underwent an autologous peripheral stem cell transplant. Optimal response was achieved with IVIg doses between 4.5-9 g/kg/month delivered at range of infusion frequencies, between twice per week and monthly (Table 1). There was marked inter-individual variation in clinical features, IVIg regimens and IgG measurements pre and post-stability.

Case 1

A 35-year old female with CIDP presented with three weeks of ascending sensory disturbance and weakness that responded to 2g/kg of IVIg. She had two similar episodes over the following nine months. At nadir she had mild (MRC score= 4 to 4+) proximal and distal, upper and lower limb weakness and impaired joint position sense (large finger movements, ankle movements) with difficulty mobilising. Nerve conduction studies (NCS) showed patchily reduced or absent sensory responses. Distal motor amplitudes were normal. There was temporal dispersion and motor conduction slowing of left median nerve at the forearm segment (distal motor latency (DML) 3.6ms, conduction velocity (CV) 41m/s from wrist to

elbow, wrist compound motor action potential (CMAP) 7mV, elbow CMAP 3.7mV). After the third episode, maintenance IVIg was commenced at 1g/kg (65g)/ month with short-lived clinical benefit lasting 4-5 days. Significant peri-dose fluctuations and activity-dependent weakness continued on 2g/kg/month. Over the following 2 years she had 2 disabling deteriorations with head drop and bulbar symptoms on 1 occasion and diplopia and limb weakness (MRC-SS= 49/70) on the other. Repeat NCS showed absent left lower limb sensory responses and reduced or borderline upper limb sensory responses (right median SNAP 4mV, ulnar 3mV bilaterally), with no evidence of neuromuscular junction dysfunction. Lower limb motor NCS were normal. Both episodes responded to an extra bolus dose of 2g/kg in addition to maintenance treatment. The addition of mycophenolate mofetil (MMF) in January 2016 and 3 courses of 2g/kg IVIg every 2 weeks markedly improved function and she returned to full-time work and regular gym attendance (Figure 1, patient 1). She initially experienced moderately severe headache requiring modification of rate of infusion, pre-medication and simple analgesics. MMF (1g bd) was weaned after 21 months as it did not facilitate a reduction in IVIg dose. An attempt at reduction of IVIg below 80g/week (5g/kg/month) in 20% decrements resulted in functionally important peri-dose fluctuation in strength, exercise intolerance, and intermittent head and finger drop at 2 months. She has tolerated this regimen for 32 months and remains stable with minimal sensory symptoms and finger extensor weakness.

Case 2

A 45-year-old man with Sjogren's syndrome was diagnosed with motor-predominant CIDP after presenting with recurrent episodes of proximal and distal weakness. NCS demonstrated normal SNAPs, CV slowing in the lower limbs (bilateral common peroneal MCV 39m/s) with proximal conduction block in both median nerves (right wrist CMAP 10mV to 2.3mV proximally, and left wrist CMAP 11.2mV to 2.7mV at Erb's point). Time to nadir was 3

months (wheelchair dependent), with IVIg (2g/kg) response lasting between 8 days to 2 months before maintenance treatment was initiated (2g/kg/month). Improvement in functionally impactful peri-dose fluctuation was achieved at 2.7g/kg/month (170g/ 3 weeks) with some residual weakness (MRC-SS= 62/70). Gradual up-titration resulted in clinical response (Figure 1, patient 2) and with correlating neurophysiological improvements (@ 2.7g/kg/month; right median CMAP 1.8mV at Erb's point, right ulnar CMAP 1.8mV at C8/T1. @4.5g/kg/month; right ulnar CMAP 3.1mV at Erb's point; @6.5g/kg/month: right median CMAP 3.5mV at elbow, right ulnar CMAP 1.6mV at Erb's point). At 9g/kg/month for 3 years (180g/week) he has maintained stable strength and function and works full time in a physically demanding job without immunoglobulin-related adverse events (MRC-SS= 63/70, MMN-RODS= 50/50).

Case 3

A 52-year old otherwise well man presented with gradually worsening paraesthesia and numbness in his hands then feet. He was diagnosed with upper-limb predominant definite CIDP. CSF protein was raised at 0.98 g/dl, initial NCS showed bilateral median sensory CV slowing (right 39m/s, left 44m/s) and ulnar sensory CV slowing (right 41m/s, left 44m/s) and reduced SNAPs (bilateral median and right ulnar SNAP 4mV, left ulnar SNAP 2mV). There was sustained gradual deterioration and evolving non-length dependent motor weakness despite 3 courses of 2g/kg of IVIg 2 months apart followed by plasmapheresis, high-dose IV then oral corticosteroids (MRC-SS= 55/70). Inherited demyelinating neuropathies were excluded (PMP22 duplication and point mutations in GJB1, BSCL2 and GDAP1) and further immunosuppression was given, IV cyclophosphamide (1.05g), Rituximab (2g), without effect. At nadir, he had dysphonia, scapular winging, bilateral wrist and finger drop (MRC-SS= 39/70). Some improvement was achieved with plasmapheresis (MRC-SS= 50/70) with further response to regular IVIg at 130g/ 2 weeks (4g/kg/month, MRC-SS= 64/70). He has

tolerated a regimen of 2g/kg/month administered as 35g/ week for 3 years with adequate, stable clinical response (MRC-SS= 68/70, CIDP-RODS= 44/48) (Figure 1, Patient 3).

Case 4

This patient's case has previously been published and will be summarised here (7,8,9). She presented acutely in 1985 at the age of 8 years, with upper and lower limb, proximal and distal weakness over 4 days. CSF protein was raised at 2.8 g/L. NCS demonstrated absent SNAPs and motor CV slowing (median DML 10.2ms, motor CV 9.5 m/s; abductor pollicis brevis CMAP 0.2 mV). On examination there was flaccid weakness affecting the upper and lower limbs, absent tendon reflexes and reduced vibration sensation. A sural nerve biopsy revealed a severe demyelinating neuropathy with onion bulb formation and T cell infiltration. Her disease has been characterised by a relapsing-remitting course consistent with CIDP, with transient but definite objective response to a range of immunosuppressive and immunomodulatory treatments including almost continuous prednisolone (15-30 mg on alternate days). Between 1988 and 1999, azathioprine (175mg daily) and beta interferon (maintenance dose of 3 million IU/0.5mL three times a week, with significant improvement at 12 weeks) were prescribed but discontinued due to side effects (azathioprine related abdominal pain and alopecia) and inefficacy; the patient continued to experience fluctuating hand and lower limb weakness requiring regular prednisolone, IVIg, and intermittent plasma exchange. From 1990 to 1995 she received over 20 courses of IVIg ranging from single infusions of 0.4 g/kg to 5-day courses of 2g/kg. A trial of methotrexate (12.5mg weekly,)see (Fialho et al. 2006) for details(19)) resulted in symptomatic improvement without change in objective assessments; cyclosporine (5mg/kg caused lymphopenia, and did not achieve clinical stability), rituximab, tacrolimus (in November 1998, dose= 3mg bd, side effects= nausea and dizziness) and mycophenolate (500 bd, ineffective in reducing frequency of plasma exchange and IVIg) were either briefly effective or ineffective. In 2006, she

underwent an autologous stem cell transplant which resulted in a sustained clinical improvement for 18 months. She was able to stop methotrexate and IVIg and reduce the dose of prednisolone by 33% to 12mg alternate days (See (Mahdi-Rogers et al. 2009) for details(20)).

In 2007, following influenza, pneumococcus, and hepatitis A vaccines for travel she experienced a relapse requiring plasmapheresis then regular IVIg infusions of 2 g/kg/week and increase of prednisolone to 15 mg on alternate days. During the following 4 years she suffered frequent relapses, with MRC-SS varying between 28/70 at worst and 52/70 at best. She received 160g of alemtuzumab in August 2008 and a further course of 180mg in April 2009 (See patient 4 in (Marsh et al. 2010) for details(21)). In 2012, she developed bilateral recurrent laryngeal nerve palsies managed with high dose but tolerated IVIg regimen (140-150g/week). In November 2013, fingolimod (0.5mg daily) was commenced which allowed slight reduction of her IVIg doses and she was relatively stable for 4 years on 130g per week (6.94g/kg/month) of IVIg and prednisolone 13mg on alternate days. At most recent review, abatacept has been started due to worsening vocal cord function and increased fluctuations in limb strength; IVIg dose remains unchanged (Figure 1, Patient 4). However, she continues to mobilise with two crutches, bilateral ankle-foot orthoses and knee brace.

Case 5:

A 41-year-old man with MMNCB presented with two years of progressive left-hand weakness, wasting, fasciculations and cramps. Initial examination revealed weakness in left finger extensors and hand grip. NCS and EMG demonstrated acute on chronic denervation of ulnar-innervated muscles and chronic denervation of median and radial nerve innervated muscles with very small CMAPs in abductor digiti minimi (ADM) (CMAP 0.6mV at the wrist, first dorsal interosseous (FDIO) CMAP 0.6mV at the wrist), with normal DML (3.2ms

and 3.3ms, respectively) and CVs (53m/s wrist to below elbow, recording at ADM). There was no conduction block. Strength improved initially with IVIg at 2g (175g)/kg/month x4 months. As per our departmental protocol, once stable improvement from baseline is achieved, we gradually down-titrate dose and frequency with regular clinical monitoring until minimal maintenance dose and frequency are established (8). At 33 months, on 1g (75g)/kg/month left-hand weakness recurred with new cramping and weakness in the right hand. The patient reported short lived symptomatic response to 1mg/kg bolus superimposed on increased maintenance dose to 1.2g/kg/month. Despite peri-dose fluctuation there was objective evidence of decline in grip strength, with right hand grip (Martin Vigorimeter) decreasing from 58kPa to 45kPa over this time correlating with new partial motor conduction block in the right ulnar nerve (CMAP at axilla 8.9mV, CMAP at Erb's point 4.8mV), a potential block in the left median distribution (CMAP at wrist 10.1mV, CMAP at elbow 7.0mV) and absent motor responses from all left ulnar innervated muscles on NCS at this point suggested undertreatment at this dose. There was improvement in right-hand grip strength to 46kPa at 5g/kg/month without adverse effect (120g, 4-weekly, with fortnightly 210g boluses for 2 doses). Stability has been maintained over 2 years (right grip strength = 58kPa) on a lower dose of 1.4g/kg/month (130g every 4-weeks) (Figure 1, Patient 5).

Case 6:

A 49-year-old man with MMNCB presented with a 1-year history of tripping followed by bilateral, asymmetric hand weakness developing over months. Examination revealed bilateral intrinsic hand muscle wasting and mild right ankle plantar flexion weakness. NCS was normal with reduced muscle activation in the right lower limb EMG (gastrocnemius and tibialis anterior). There was no evidence of conduction block. He responded initially to 2g/kg/month (140g/ 5 weeks) achieving good response after 6 months: MRC-SS= 69, MMN-RODS= 36-41, right grip strength= 72kPa, left grip strength= 36kPa). This improvement was

maintained for 7 years on 1g/kg/month (80g/6 weeks) administered at home via implanted venous access device. On attempted dose reduction he deteriorated on 0.4g/kg/month, MRC-SS= 62 and MMN-RODS= 32 but re-stabilised on his previous maintenance dose after 1, 2g/kg bolus. 2 years later, his IVIg response became brittle and remained so despite up-titration to 2g/kg/month: R grip strength increased from 7kPa pre-treatment to 85kPa day 3 post treatment, L grip from 30kPa to 90kPa. CT/PET scan was negative for occult malignancy, blood tests excluded metabolic, infective, nutritional or neoplastic cause for deterioration. Subjective and objective stabilisation (MRC-SS= 70, right grip strength= 50kPa, left grip strength= 63kPa) was achieved at 4.5g/kg/month (250g, 4-weekly for 2 months) without adverse event. This has been maintained for 9 months at the lower dose of 2.6g/kg/month administered as 45g of IVIg weekly at home.

Serum IgG levels

Median pre-dose (trough) serum IgG levels were significantly higher than upper limit of normal in all patients once clinically stable on optimal IVIg regimen (Table 1, Figure 2). There was no clear correlation between IgG level and either dose or clinical status. Where data was available, no difference was found between pre and post-stabilisation peri-dose (pre and immediately post dose) IgG levels.

Discussion

These six cases demonstrate the heterogeneous presentations and variation in treatment response to IVIg between patients with CIDP and MMNCB and within individuals over time. All patients showed clear objective evidence of response to IVIg treatment but at some point required higher doses than those used in clinical trials to achieve and maintain remission. There are many factors that influence IVIg response, including clinical presentation, dose and frequency of administration. This case series supports the measurement of clinical impairment, as well as activity and participation to assess treatment response, rather than

titration according to serum IgG levels, as a better guide to optimal dosing.

There is ongoing debate about the use of IgG in patient monitoring with conflicting evidence about whether the absolute IgG or the change in IgG with treatment determines response to IVIg (Table 2) (22). Compared to another study of 25 CIDP patients with active but stable disease, our pre-dose, (trough) IgG levels in stability were significantly higher (15g/L compared with 46g/L in our group) (23). It is difficult to compare post infusion IgG levels between studies where post-infusion measurement were taken at different time points (Table 2) (17). Absolute serum IgG levels are unlikely to represent all of the complex immunomodulating cascade of events triggered by an infusion of IVIg, or the pharmacokinetics, which are concentration dependent, of this plasma protein in different individuals are concentration dependent (24,25). While biomarkers such as IgG may potentially be helpful, they would be an addition rather than a replacement for subjective and objective clinical markers and the relationship between serum IgG levels and clinical response is still being established.

The motor subscale of the NIS (NISm) and the MRC are the two most commonly used grading systems for manual muscle testing, and we use the MRC-SS, modified to include FDIO, making the maximum score 70 (26). Both scores have been criticised for their inadequate psychometric properties. However, taking these limitations in to account, the use of MRC-SS over years in our cases demonstrates stabilisation of strength with the use of high-dose IVIg (figure 1) (26).

Most of these cases were otherwise fit people prior to their disease. Connecting impairment, measured through MRC-SS and grip strength, disability measured by the ODSS, and handicap measured by the Rotterdam nine items handicap scale has been investigated by Merckies et al(27). They showed that combining impairment and disability measures explained more than 75% of the variance in their handicap measure (27). This also highlights

that participation in society cannot be completely explained by our current outcome measures and other, unexplained and person-specific factors play an unmeasurable and variable role.

This is highlighted by the variable relationship between MRC-SS, grip strength, and RODS scores within our six patients, which are measurements taken at one time point.

Reduced exercise tolerance is difficult to capture using the Inflammatory-RODS and MMN-RODS given disease fluctuations and infrequent routine clinical review. The mechanism of reduced exercise tolerance may be dynamic; exercise-induced conduction block can occur in both MMN and CIDP (28). The best marker in these patients of their activity and participation is their return to their baseline roles and hours at work, which is an independent marker of quality of life (29).

Repeatable, responsive, and easy to acquire biomarkers would greatly aid in the clinical management of patients with inflammatory neuropathies. Neurofilament light chain (NfL) has recently been evaluated as a biomarker in inflammatory neuropathies, and has a well-established role in other acquired and genetic neurological conditions (30). One group has shown that serum NfL levels are significantly higher in un-treated patients with CIDP than healthy controls, but not in CIDP patients on maintenance treatment. Also, serum NfL levels normalised in 83% of newly treated patients who were also deemed clinical responders to treatment (31). In another study of patients with a range of inflammatory neuropathies, a significant correlation was noted between serum NfL and overall neuropathy limitations scale (ONLS) at sampling and at follow-up, which reinforces the potential for NfL to be a responsive, clinically-relevant, repeatable biomarker (32).

Our six patients tolerated frequent, high doses of IVIg remarkably well, and the only adverse effect experienced was transient but moderately severe headache. However, rare, serious side effects including aseptic meningitis, renal impairment, thrombosis, and haemolytic anaemia have been reported (33). There is conflicting evidence about whether the risk of developing

these side effects correlates with dose of IVIg. Rajabally et al. reported that a daily dose greater than 35g of IVIg resulted in a higher risk of thrombotic events and another large retrospective, UK study found clinically significant Ig-related haemolysis occurred in association with induction bolus doses only (34,35). The same study revealed Ig-related biochemical changes in haemoglobin and sodium without clinical effect occurred more commonly in individual with low pre-treatment haemoglobin or those on concomitant medication which can contribute to hyponatraemia (35). A study in our neuromuscular cohort did not find a difference in IVIg doses between the group of patients experiencing a thromboembolic event and those who did not (34,36). Therefore, immunoglobulin related thrombotic risk is likely dependent on individual, yet unidentified factors rather than IVIg regimen.

Conclusion

We present six unusual cases of chronic, acquired, demyelinating neuropathies which have had an aggressive course resulting in disability in otherwise, fit and previously active patients. These patients consistently and reliably respond to very high-dose IVIg, failing to respond to conventional doses and have required an individualised treatment regimen that has not and could not practically be replicated in a clinical trial. No Ig-related adverse events occurred in these patients despite very high dose at high frequency, in some cases for prolonged time period suggesting the Ig-related complications are influenced by risks in the individual as well as dose and rate of IVIg itself. Their disease activity highlights the difficulties in managing refractory forms of these diseases, and encourages ongoing research into the pathophysiology, drug dosing trials, and real-life application of outcome measures.

Table 1: Summary of clinical features and IgG measurements before and after achieving clinical stability

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6	
Diagnosis	Definite CIDP		Definite MMN		Definite CIDP		Definite CIDP		Definite MMN		Definite MMN	
Age of onset	35		37		41		8		39		47	
Type of onset	Acute		Chronic		Chronic		Acute		Chronic		Chronic	
Previous treatments	MMF, PE		IV CCS		PE, oral and IV CCS, IV CPH, rituximab		AZA, β -I, MTX, CYC, rituximab, tacrolimus, MMF, ASCT, PE, oral CCS, A-Mab, fingolimod, abatacept					
Dose of IVIg required for stability	80g/week 5g/kg/month		180g/week 9g/kg/month		4g/kg/month, <i>(current maintenance: 2g/kg/month)</i>		90g bi-weekly 6.94g/kg/month		5g/kg/month <i>(current maintenance: 1.4g/kg/month)</i>		4.5g/kg/month <i>(Current maintenance: 4.2g/kg/month)</i>	
Pre and Post Stability Measurements	Pre	Stable	Pre	Stable	Pre	Stable	Pre	Stable	Pre	Stable	Pre	Stable
MRC-SS	69	67	60	63	39	68	Fluc.	47 with fluc.	67	56	67	56
Median IgG (g/L)	36	46	44	55	24	35	48	49	13	23	ND	ND

MMF = mycophenolate mofetil, PE = plasmapheresis, IV = intravenous, CCS = corticosteroids, CPH = cyclophosphamide, AZA = azathioprine, β -I = beta-interferon, MTX = methotrexate, CYC = cyclosporine, ASCT = Autologous peripheral blood stem cell transplantation, A-Mab = alemtuzumab, MRC = Medical Research Council Sum Score (maximum 70), CSF = Cerebrospinal fluid, fluc. = fluctuations

Table 2: Studies that have used blood IgG as a biomarker in patients treated with immunoglobulin.

Study	No. of Patients	Condition	Mean Age (years)	Duration of Disease (years)	Ig Dose (g/kg/month) (method of administration)	Pre-IgG (g/L) Mean (SD)	Post-IgG (g/L) Mean (SD)	Comment
(37)	29	CIDP	53.4	4.6	0.31 (IV)	13.9+/- 3.6	22.05 +/- 3.85	After 10 weeks of SCIG; IgG 18.4 +/- 5.2 g/L
(38)	6	MMN		First IVIg cycle	2 (IV)	13.2 +/- 1.78	34.9 +/- 2.67	Follow up: 39 MMN patients receiving IVIg maintenance therapy; median IgG =18.7 g/L (range 12.6–35.6 g/L)
(39)	23	MMN	41 (24–55)	First IVIg cycle	2 (IV)	13.6 (4.7)	36.9 (7.8) Taken day 5 of IVIg course	No correlation between total IgG levels at baseline, at day 1 and day 5 of treatment. Mean ΔIgG levels were not statistically significantly higher in IVIg responders than in non-responders at all time points.
(40)	8	MMN	57.3	6.3	1.09 +/-0.56 (IV dose transferred to equivalent weekly S/C dose)	17.5 +/- 4.9		Median IgG concentration 16.8 +/- 5.0g/L post 24 weeks of SCIG
(41)	5	MMN	57 (47-65)	14 (8-25)	0.46 (0.27-0.62) (IV dose transferred to equivalent weekly S/C dose)		After 20 weeks of SCIG, mean IgG 15.8, (13.8 – 17.4)	
(42)	1	MMN	63	1	0.8-1.1 (IV dose transferred to equivalent weekly S/C dose)		After 6 months of SCIG, IgG= 21 g/L	Patient initially deteriorated, requiring a dose increase of 25% of total monthly dose. IgG level at deterioration= 15 g/L
(23)	25	CIDP		mean 5 (5 months to 13 years)	52.9g/month (14.9g) (IV)	15.0; IQR= (13–17)	21.4 (2.63)	IgG levels were determined in serum samples obtained immediately before and 5 min after every infusion. ΔIgG mean= 7.8 g/l; (IQR 6–9). Post-treatment IgG levels and ΔIgG levels were statistically significantly related to the IVIg dosage administered per infusion.
(24)	9	CIDP	55.8	6.61	0.89 (0.28)	16.7 (3.4)	33.7 (3.4)	Samples obtained before and immediately after IVIg treatment
(43)	15	CIDP	59.5 (36–75)	9.07 (4–26)	83.67g (range 25–125g). Mean interval between infusions= 4.47 weeks (2–10)	15.2	19.5	These were defined as the percentage increases in IgG levels 14 days following completion of two different infusions in each patient.
(44)	2	CIDP	47.5	9.5	Patient 1 range: 1.32-1.7 Patient 2 range: 1.2-2	Patient 1 Unstable: 10.95 (7.45-1.15) Patient 2 Unstable: 1.33 (1.25-1.44)	Patient 1 Stable: 17.60 (17.20-20.34) Patient 2 Stable: 18.41 (16.48-19.01)	
(45)	4	CIDP	43.5	3.4	3	Optimum IgG mean= 32		Relapse IgG level mean = 4.5 g/L

Contribution= AS. Carr designed the study. M. Kapoor collected the data, performed the statistical analysis, interpretation of the data and wrote the first draft. All other authors provided patients for inclusion and provided detailed written edits and multiple further drafts of the review for publication.

Affiliations= MK gratefully received funding from a patient's bequest. MM Reilly is grateful to the Medical Research Council (MRC), MRC Centre grant (G0601943), the National Institutes of Neurological Diseases and Stroke and office of Rare Diseases (U54NS065712) for their support. MM Reilly, MP Lunn and AS Carr are supported by the National Institute of Health Research, University College London Hospitals, Biomedical Research Centre.

Acknowledgements: The authors thank A. M. Rossor for his assistance in preparing the figure for Case 4.

The authors report no disclosures relevant to the manuscript.

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