Routine blood monitoring in maintenance Immunoglobulin treatment of inflammatory neuropathy: is it clinically relevant?

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Abstract

Background

Pre-treatment screening for IgA deficiency and close monitoring of full blood count (FBC) and urea and electrolytes (U&E) is recommended with intravenous immunoglobulin (IVIg) therapy in neurological diseases.

Aims

To examine the frequency of biochemically defined and clinically significant episodes of treatment associated haemolysis, neutropenia, thrombocytopenia and acute renal impairment in a cohort of patients on maintenance Immunoglobulin (Ig) therapy for inflammatory neuropathy.

Methods

A retrospective review of routine blood monitoring in a cohort of patients from two UK specialist peripheral nerve centres. Accepted definitions for clinically and biochemically significant haemolysis, neutropenia, thrombocytopenia and acute kidney injury (AKI) were used.

Results

1919 infusion episodes in 90 patients were analysed. Age (mean(S.D))= 58.09(14.4)years, 63% male, 72% CIDP (28% MMN), 97% IVIg (3% SCIg). Dose= 1.57 (0.79) g/kg/month or 97.1(37.3)g/infusion, frequency: 3.9 (1.4) weeks.

Relative IgA deficiency was noted in 2 individuals (prevalence: 2.2%, 95% C.I.: 0-5.2) who received a combined total of 38 infusions (3800g IVIg) without adverse event. No clinically significant episodes of haemolysis, neutropenia, thrombocytopenia or AKI occurred in relation to treatment. An asymptomatic drop>10g/L haemoglobin (Hb) occurred in 3.5% (95% CI: 2.7-4.3) of treatment episodes in 38 individuals, mean reduction: 17.7(7.4)g/L; lowest Hb: 86g/L. Lower pre-treatment haemoglobin correlated with risk of recurrent episodes Ig-related drop (p:0.007). Two patients with chronic renal failure (stage 1 and 3) had received 28 (IV) and 104 (SC) infusions respectively, (6416g Ig) without impact on estimated glomerular filtration rate (eGFR).

Conclusions

No clinically significant Ig-related events were identified in this representative cohort. We suggest annual screening or clinically indicated testing as safe and more appropriate in long-term Ig use. Screening for IgA deficiency and baseline FBC and U&E may be helpful in identifying those at greater risk of complication.

1. Introduction

Intravenous immunoglobulin (IVIg) treatment in Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) and Multifocal Motor Neuropathy (MMN) results in meaningful improvement of symptoms and function in the majority of cases [1,2]. Regular infusions are often required as maintenance therapy, usually lifelong in MMN, and long-term treatment in all but 40% of CIDP patients in whom the disease may remit spontaneously [3]. The safety profile is therefore important to consider in the context of cumulative doses over many years.

Long term IVIg is considered safe, and sometimes chosen over steroid treatment in CIDP for this reason [4]. Mild, transient adverse reactions are seen in 10-15% of patients and include flushing, changes in heart rate and blood pressure, rash and headache. Often these symptoms can be modified by reducing the rate of infusion and fractionating the dose. However, potentially serious adverse reactions occur at a frequency of approximately 1% [5]. Reported events include renal impairment, haemolysis, anaphylaxis, aseptic meningitis and thromboembolic events [5,6,7]. However, there are a number of reasons that suggest this information may be out of date or not directly applicable to the inflammatory neuropathy cohort.

Firstly, IVIg-related renal impairment was seen almost exclusively with sucrose-containing products which are no longer in widespread use [7]. Secondly, anaphylactic reactions reported in individuals with absolute IgA deficiency in the immunoreplacement setting have been addressed in the production process with very low IgA levels in currently available products: 165-820ng/mg of IgG [8,9]. Although relative IgA deficiency can occur in the immune-competent the theoretical risk of anaphylaxis is not the same. However, it must be noted that anaphylactic reactions may occur with relative IgA deficiency (0.4% general population) and IgA replete individuals [6,10]. Thirdly, it is well recognised that although minor fluctuations in haemoglobin (Hb), platelet and white cell counts do occur, they are rarely clinically significant [7,11].

The EFNS guidelines for IVIg use in neurological diseases recommend careful monitoring of FBC, and U&E, [11,12]. The historical approach in our institutions was to check pre-treatment IgA, Hepatitis B (HBV) and C (HCV) status, routinely monitor FBC and U&E on day 1 of each treatment episode, and consent for a <1% risk of serious adverse events as listed above [13]. This reflects common practice in specialist peripheral nerve services within the UK National Health Service (NHS). We will explore the clinical relevance of this approach to safety monitoring in patients with inflammatory neuropathy on Ig maintenance therapy.

2. Aims and Methods

Our aim was to examine the frequency of biochemically defined and clinically significant episodes of IgA deficiency/ IgA-related anaphylaxis, haemolysis, neutropenia, thrombocytopenia, acute renal failure and hyponatraemia in this patient cohort.

We identified a subset of inflammatory neuropathy patients on maintenance IVIg or SCIg therapy attending either the National Hospital for Neurology and Neurosurgery, London (NHNN), or the Manchester Centre for Clinical Neuroscience (MCCN) for infusion on at least one occasion between September to November 2017. All patients were diagnosed with probable or definite CIDP or MMN in accordance to EFNS/PNS Diagnostic Criteria [1, 2] and managed by a consultant with a specialist interest in peripheral nerve disease.

All included individuals were clinically stable on maintenance Ig therapy [14]. Basic clinical and demographic data were collected alongside IgA status taken prior to first treatment. Haemoglobin (Hb, g/L), Platelet count (Plt, 10^9/L), Neutrophil count (Ne, 10^9/L), Sodium (Na, mmol/L), Urea (mmol/L), Creatinine (Cr, µmol/L) and estimated Glomerular Filtration Rate (eGFR, mL/min/1.73m2) for all pre-infusion FBC and U&E samples were reviewed. Results were compared to that taken on the preceding treatment episode and pre-treatment baseline. Accepted definitions for biochemically significant IgA deficiency, haemolysis, neutropenia, thrombocytopenia and renal impairment were used [Table 1, 15-26]. Contemporaneous medical notes were reviewed when any result met criteria for biochemical significance to look for clinical manifestations.

Data were collected retrospectively by case note review of routine clinical practice and therefore covered by University College London Hospital (UCLH) Trust and Salford Royal Hospital trust governance policies.

Statistical analysis were performed on Microsoft excel. Risk of biochemical or clinically significant events were calculated as proportions with 95% confidence intervals according to Poisson distribution. When zero events were captured, Hanley's simple formula was used to calculate upper limit of 95% CI for rate of occurrence [27]. T- tests were performed to assess differences between groups, $p>0.05$ was chosen as statistically significant.

3. Results

We included 90 patients who had received a total of 1919 infusions. Mean age (S.D., range) at time of data collection was 58.1 (16.3, 14-42) years. 63 (70%) were male and 27 (30%) were female, 65 (72%) CIDP, 25 (28%) MMN. 87 (97%) of the patients were treated with IVIg with a mean (SD) dose of 1.57 (0.79) g/kg/month at a median frequency of every 4 weeks (range 2-7 weeks). Three (3.3%) were treated with subcutaneous immunoglobulin (SCIg) with a mean (SD) dose of 1.5(0.5) g/kg/month with regular weekly infusions. Mean (S.D) duration of Ig treatment was 18 (8.9) months.

Relative IgA deficiency (IgA = 0.38 g/L and 0.64 g/L respectively) was noted in 2 individuals, prevalence rate 2.2% (95% C.I.: 0-5.2%) (Table 1). No anaphylactic reactions occurred in any individual: 0% (95% CI: 0-2.2). The individuals with relative IgA deficiencies received 12 (1200g IVIg) and 26 (2600g IVIg) infusions respectively without adverse event; rate of clinically significant event in at risk individuals: 0% (95% CI: 0-7.9%). No individuals with absolute IgA deficiency were identified.

Table 1. **Risk of Ig-related complications.** Prevalence rates given with 95% confidence intervals (CI) as per Poisson distribution. IgA deficiency: immunoglobulin A deficiency, Hb: haemoglobin, NE: neutrophils,PLT: platelets, Na: sodium, AKI: acute kidney injury. Definitions for clinically and biochemically relevant lower limits of normal (LLN) are provided [15,16].

			Risk per individual exposed	Risk per infusion
			% (95% CI)	% (95% CI)
N			90	1919
IgA deficiency	Biochemical definition	<**LLN*: 0.7g/L** [15]	2.2% (0-5.5)	
	Clinically significant	**<0.05g/L** [17]	0% (0-2.2)	0% (0-0.1)
Hb	Biochemical definition	>**10g/L↓** [18]	42.2% (28.8-55.6)	3.5% (2.7-4.3)
	Clinically significant	**<70g/L with symptoms** (fatigue, weakness, dizziness, reduced exercise tolerance, shortness of breath, changes in mental status, muscle cramps, and angina or severe congestive heart failure) [19] · **70-90g/L** with symptoms if cardiac disease[19]	0% (0-2.2)	0% (0-0.1)
NE	Biochemical definition	**0.5-1.0x10^9/L**: mild-moderate neutropenia (low risk of infection) [20]	3.3% (0-6.7)	0.6% (0.2-1.0)
	Clinically significant	**<0.5x10^9/L**: severe neutropenia (high risk of infection) [20,21]	0% (0-2.2)	0% (0-0.1)

PLT	Biochemical definition	<**LLN* (150 x10^9/L)** [16]	5.6% (0.7-10.5)	2.2% (1.5-2.9)
	Clinically significant	**<10 x 10^9/L** [19,22,23]	0% (0-2.2)	0% (0-0.1)
Na	Biochemical definition	<LLN* (135 mmol/L) [15]	33.4% (22.1 – 45.5)	15.5% (13.7 – 17.3)
	Clinically significant	Na <135mmol/L AND symptoms directly attributable to hyponatraemia (confusion, cardiorespiratory distress, abnormal and deep somnolence, seizures, GCS ≤9) [24]	0% (0-2.2)	0% (0-0.1%)
AKI	Biochemical definition	AKI= **1. Rise in serum creatinine of 26 micrograms/ml** *or more in 48 hours, or* **2. 50% or greater rise in serum creatinine** *known or presumed to have occurred in past 7 days, or* **3.** *Fall in urine output to <0.5ml/kg/hr for over 6 hours* [25]	0% (0-2.2)	0% (0-0.1)
	Clinically significant	Stage 3 AKI: · **≥200% rise in serum creatinine** *from baseline within 7 days* (≥3.00 × baseline) · For acute injury with pre-existing chronic kidney disease: **Current creatinine ≥354 µmol/L** *with either* **Rise of ≥26 µmol/L** within 48 hours *or* **Rise of ≥50% from baseline** within 7 days · Any requirement for renal replacement therapy · *Urine output <0.3 mL/kg/h for 24 hours* · *Anuria>12* hours [26]	0% (0-2.2)	0% (0-0.1%)

There were no clinically significant episodes of haemolysis, neutropenia, thrombocytopenia, hyponatraemia or renal impairment in relation to immunoglobulin treatment in this cohort.

Individual risk: 0% (95% CI: 0-2.2), risk per infusion: 0% (95% CI: 0-0.1) although some treatment-related fluctuations meeting criteria for biochemical significance did occur.

Thirty eight (38) individuals (42%, 95% CI: 28.8-55.6) had a biochemically significant drop in haemoglobin associated with 68 of 1919 infusion episodes (3.5%, 95% CI: 2.7-4.3). Mean (SD) Hb reduction between treatments in these individuals was 17.7 (7.4)g/L. The lowest Hb recorded was 86g/L. 28/38 individuals had one isolated occurrence of low haemoglobin. Baseline characteristics of these patients were similar to the general cohort: mean (SD) age =60.13 (12.8) years, 28 (74%) male and 10 (26%) female, 30 (79%) CIDP and 8 (21%) MMN. Their mean (SD) dose was 1.78 (0.91) g/kg/month. Multiple episodes (40 events) of Ig-related fall in Hb were recorded in 10 individuals. The mean pre-Ig Hb level was lower in this group (133.3. g/L versus 144.5g/L, p = 0.007), there were no other differentiating features between those with multiple versus one isolated episode of Ig-related drop in Hb. Where tested, markers of autoimmune haemolysis were not found. This included bilirubin (15 individuals), direct Coombs test (9 individuals) and lactate dehydrogenase (7 individuals, with nonspecific increases to 260 and 314 IU/L in 2 individuals (reference range <225 IU/L [14]).

Biochemically defined neutropenia (range: 0.7-0.99x10^9/L) without clinical correlate occurred in three individuals (3.3%, 95% CI: 0-6.7%) over 12 infusions (0.6%, 95% CI: 0.2-1.0%) of. Of note one individual was on concomitant mycophenolate and the neutrophil count normalised on discontinuation of this drug. Another individual prone to neutropenia had been previously treated with cyclophosphamide and azathioprine. Hb (86-107g/L) and platelet count (55-80x10^9/L) were both chronically low with some asymptomatic and self-correcting infusion-related fluctuations over many years. Investigation excluded primary haematological causes.

Five individuals (5.6%, 95% CI: 0.7-10.5) had infusion-related thrombocytopenia on 49/1919 infusions (2.2%, 95% CI: 1.5-2.9). One person had an isolated episode of mild thrombocytopenia (140 x10^9/L) with spontaneous normalisation. Another four had mild chronic thrombocytopenia over a total of 48 infusions fluctuating between 100-141 x10^9/L and not progressing over time.

Thirty-one (31) individuals (33.4%, 95% CI: 22.1 – 45.5) had 299 episodes of hyponatremia (15.5%, 95% CI: 13.7 – 17.3). The majority of occurrences (267/ 299: 89.3%) were mild fluctuations outside normal range: 130-135mmol/L. 149/299 events occurred in two individuals with Ig-unrelated alternative explanations for low sodium: (i) previous neurosurgical removal of meningioma with chronic pre-treatment hyponatraemia, (ii) concomitant bendroflumethiazide 2.5mg OD, sodium improved on discontinuation this drug. A sodium level below 130mmol/L occurred with 32 infusions, 81% (26/32 infusions) accounted for by the two individuals described above. The majority of individuals with at least one episode of hyponatraemia were on a concomitant medication that is known to cause hyponatraemia.

Two (2) individuals with chronic renal impairment received regular Ig without decline in eGFR. One with stage 1 chronic renal failure received 28 infusions of 120g IVIg 4-weekly. The second had type 1 diabetes mellitus and acquired stage 3 acute kidney injury secondary to a previous episode of diabetic ketoacidosis (DKA) secondary to sepsis. Creatinine remained stable between 200 and 300µmol/L over a one year period on weekly SCIg (24g). There were no episodes of Ig-related AKI or Ig-related acute–on-chronic renal impairment in this cohort.

Moreover large numbers of individuals are treated with maintenance IVIg in both institutions: 119 (SRH) and 201(NHNN) in 2018; 153 and 201 in 2017, 146 and 206 in 2016 (average 342 patients per year), at a mean frequency of 4.3 weeks and cumulative dose of 95,000g (SRH) and 204,924g (NHNN) in 2018, 108,000g and 206,875g in 2017, 106,000g and 177,940g in 2016. Despite these high volumes the peripheral nerve clinical teams are not aware of any episodes of IVIg-related renal impairment and only 3 cases of clinically relevant haemolysis in either centre in the past decade (risk of clinically significant haemolysis: 0.007% (95% CI: 0-0.015%) per infusion) Risk per individual could not be calculated because these numbers represent all Ig usage in our departments including bolus treatment of monophasic autoimmune disease (GBS) and maintenance treatments as examined here in more detail. Interestingly, all cases of haemolysis occurred in the context of induction doses of IVIg (2g/kg/3-5 days), developed minimal symptoms of fatigue within 4-7 days with spontaneous resolution of clinical and biochemical abnormalities within a maximum of 3 weeks. No transfusions or corticosteroid treatments were required. All 3 individuals now tolerate regular subcutaneous Ig (SCIg) at fractionated doses at weekly intervals and remain clinically stable from a neuropathy perspective for between 1 and 4 years.

4. Discussion

In this retrospective observational study of maintenance immunoglobulin treatment for inflammatory neuropathies in two separate UK specialist services there were no clinically significant episodes of haemolysis, neutropenia, thrombocytopenia, hyponatraemia or renal impairment during 1919 infusion episodes in 90 individuals. Routine monitoring revealed a biochemically significant drop in Hb in 3.5% of infusion episodes triggering further investigation but no intervention. Hyponatraemia without clinical symptoms was picked up in 15.5% of infusions, but this phenomenon was not definitely related to Ig treatment. Two individuals with stage 3 CRF tolerated regular Ig treatment (for 12 and 18 months respectively) without detectable Ig-related impairment of renal function. This suggests that routine monitoring of FBC and U&E is not clinically relevant in this setting

Within our patient group we did observe relatively high rates of infusion-related fluctuation in Hb (42%) and sodium levels (34%), with recurrence of these findings on multiple occasions in the same individuals. This suggests the risk of drop in Hb or sodium is related more to individual factors than exposure to Ig, although Ig may play a role. Those prone to recurrent episodes of biochemically significant drop in Hb had a lower pre-Ig Hb baseline and those prone to hyponatraemia were more likely to be on another medication which can contribute to low sodium. Therefore screening FBC and U&E pre-treatment is probably sensible to identify at risk individuals. Although we did not identify any clinical significant episodes of haemolysis, neutropenia, thrombocytopenia, hyponatraemia or AKI in this study this does not mean that the Ig-related risk of these complications is zero [27]. The 95% confidence intervals reported in the table provide an estimate as to the accuracy of the rates observed here and allow for some extrapolation to real life clinical practice based on number of patients treated, relevant personal factors of the individual and frequency of Ig infusion.

We acknowledge that numbers are too small to interpret a definite relationship; however it is interesting that the only clinically significant episodes of haemolysis in our two centres over the past 10 years occurred in the context of IVIg induction treatments. It may be that the risk is higher on

initial treatment or related to higher doses given at induction (2g/kg) compared to those for long-term maintenance (average: 1.5g/kg/month). Therefore, it remains important to counsel for a ~1% risk of haemolysis in the consenting process even if the risk in maintenance treatment is significantly lower in this stud y[28].

We estimate the risk of Ig-related AKI as 0-0.1%, an order of magnitude lower than that reported in the historical literature: 0.77% (1 in 130 patients treated for GBS [29]). The decline in use of sucrose-containing Ig products may explain this difference. This is supported by a study on a group of 174 patients on maintenance immunomodulatory IVIg for pemphigus over 10 years in which the rate of ARF in the non-sucrose-containing products was 1000 times lower than in those treated on sucrose-stabilised IVIg (0.55% and 0.0001% [30]). Levine et al suggest IVIg-related decline in renal function with cumulative treatment reporting ≥20% decline in GFR in 10% of their cohort [7]. Absolute values of GFR were not stated and it is unclear if criteria for chronic renal impairment were met during the monitoring period. We did not observe this pattern in either of the individuals with CRF described.

5. Conclusion

We no longer perform routine pre-infusion monitoring of FBC and U&E in our patients on maintenance IVIg therapy and we suggest that appropriate blood tests are performed either when clinically indicated or at annual follow up assessment. Pre-immunoglobulin screening for IgA deficiency and baseline FBC and U&E is sensible to identify those as higher risk of adverse events although no clinically significant events occurred within this cohort even when biochemical markers were breached, so the actual risk remains small. This information is reassuring regarding the reduced access to safety monitoring associated with transfer to home-based treatment with subcutaneous immunoglobulin therapy (SCIg) which is likely to follow on from the PATH study which showed efficacy of SCIg as a maintenance therapy in CIDP [31].

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