Immunoglobulin shortage: Practice modifications and clinical outcomes in a reference centre

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ABSTRACT

Background. – Growing numbers of indications for intravenous immunoglobulins (IVIg) in recent years has resulted in an increase in the consumption of these products. A lack of raw material has led to IVIg shortage. The objective of this work was to evaluate the impact of this situation on patient care in one French referral centre considering practice modifications and clinical impact.

Methods. – All patients treated with IVIg for chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and myasthenia gravis from October 2017 to October 2018 were included.

Results. – Out of 142 patients, 111 (78%) had a modification of their IVIg treatment. We noted that 75 (68%) patients had a delay in IVIg treatment, 41 (37%) patients had a decrease in IVIg doses and 31 (28%) experienced IVIg treatment interruption. Thirty percent of patients for whom IVIg treatment was discontinued were switched to other treatments mainly plasma exchange (16%) or corticosteroids (13%). Switches to plasma exchange or corticosteroids were carried out in order to save immunoglobulins for patients who had no other alternatives. Fifty-eight (52%) patients presented a deterioration of their clinical score after IVIg treatment changes including 31 (28%) patients who had a moderate or a clinically significant deterioration. Concerning practice modifications, we noted a substantial though not significant decrease in median IVIg dose for myasthenia gravis and a significant increase in the delay between IVIg courses for chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy ($P = 0.011$ and $P = 0.018$ respectively).

Conclusion. – Our study showed a rather important number of changes in IVIg treatment related to IVIg shortage during the period considered. These changes had a negative impact on the clinical status of some patients.

1. Introduction

Immunoglobulins (Ig) are therapeutic preparations obtained from blood plasma [1]. Ig use began in 1950, first by intramuscular injection, then at the beginning of the 80s intravenously in replacement therapy for primary immunodeficiency [2]. In 1981, Imbach et al. noticed their efficiency in treating immunological thrombocytopaenic purpura. This discovery made it possible to use Ig for autoimmune and inflammatory diseases [1,3].

For a few years now, the use of Ig has been steadily increasing worldwide. Over the last 15 years, the demand has risen three-fold [4,5], with a great increase of consumption in emerging countries throughout Asia and the Middle East [6]. In France, the use of Ig increases also every year, with an average rise of about 10% per year [7]. This phenomenon can be explained by expanded indications these last years, mainly in immunomodulatory therapy with over a hundred pathologies involved. Yet, few of these indications get a market authorisation; today off-label indications represent 50% to 70% of the demand for intravenous Ig (IVIg) [8].

Recently, the third National Ig Database Report of the British National Health Service pointed out that neurologic indications are, at the moment, the main reason internationally for the use of IVIg [4].

Immunomodulatory doses of IVIg given for autoimmune or inflammatory diseases are four or five times higher than the doses used in replacement therapy for primary and secondary immune deficiency with a total dose of 1–2 g/kg of IgG injected within 2–5 days per month [9].

This is why the improvement and harmonisation of Ig use in neurology is a real concern within our university centre and requires an evaluation of professional practices.

This increasing demand associated with the limited supply of the raw material has caused problems of procurement and international shortage [4]. In France, the shortage was particularly worrysome at the beginning of 2018, related to production restrictions of the largest pharmaceutical group. These tensions were to be exacerbated in the coming months due to a shortage of blood and plasma collection because of the coronavirus disease 2019 (COVID-19) crisis.

A review on the impact of drug shortages on patient outcomes, published in 2019, reported that drug shortages had negative clinical, economic and humanistic consequences for patients. However, there were no reports on IVIg [10].

The objective of our study was to assess the impact of IVIg shortage on patient care and to evaluate the clinical consequences.

2. Patients and methods

2.1. Study design

This was a retrospective, single-centre study, conducted from October 2017 to October 2018, in the department of neuromuscular diseases at the University Hospital, la Timone, Marseille, France. We assessed patient data one year before the shortage, in 2016, and one year after the shortage, in 2019.

The study included all patients given IVIg for chronic inflammatory demyelinating polyneuropathy (CIDP), Lewis and Sumner syndrome (LSS), multifocal motor neuropathy (MMN), or myasthenia gravis.

We excluded: patients with incomplete data; deceased patients; patients not monitored during the period under consideration for indirect impact analysis.

Data were collected by AXIGATE® (university centre database) and were supplemented with medical records and diaries in Pharma® software (Computer Engineering, version 5.9). This software has been used in our hospital pharmacy since 2010 to store and record drugs delivered to inpatients and outpatients and in care units to track prescriptions and drug administration.

2.2. Data collection and analysis

IVIg treatment (IVIg type, dose and infusion regimen) and patient data (sex, weight, and disease) were anonymised to maintain confidentiality and collected in an Excel table.

When evaluating the impact of IVIg shortage, we noted three types of treatment changes:

- decrease in IVIg dose;
- discontinuation of IVIg treatment and;
- IVIg treatment delay.

IVIg treatment delay was defined as at least a 7-day delay between two courses for regimens scheduled for four weeks and at least a 3-day delay for regimens scheduled for less than four weeks. The events studied were the number of types of changes (decrease in IVIg dose, delay in IVIg treatment, discontinuation of IVIg treatment) for each patient to assess the impact on patients' IVIg courses.

The median IVIg dose and the median delay between two IVIg treatments were compared between 2016 and 2019, i.e. one year before shortage and one year after shortage, for each dysimmune neuromuscular disease separately, in patients followed between 2016 and 2019.

In addition, scores on the following clinical scales were collected for all patients: Rasch-built overall disability scale (RODS) and overall neuropathy limitation scale (ONLS) for CIDP and LSS, Rasch-built overall-disability scale (MMN-RODS) for MMN and myasthenia muscle scale for myasthenia gravis [11,12]. Each patient's functional scores were averaged; then, deviation from the mean was determined after each prescription change. Clinical outcomes were evaluated for each patient by expert analysis (S.A).

The RODS was scored on 48 points and then recalculated on 100 points. The MMN-RODS was scored on 50 points and then recalculated on 100 points [11,12].

For data analysis purposes, the patients were divided into three groups:

- Group 0: Low score deterioration, according to our considerations and those of the medical team, i.e. slight but stable discomfort: ONLS score (unchanged); RODS score (decrease < 4 points); myasthenia muscle score (decrease < 5 points);

- Group 1: Moderate deterioration: ONLS score (increase = 1 point); RODS score (decrease $\geq$ 4 and $<$ 6 points); myasthenia muscle score (decrease $\geq$ 5 and $<$ 10 points);
- Group 2: Clinically significant deterioration, according to our consideration: ONLS score (increase $\geq$ 2 points); RODS score (decrease $\geq$ 6 points); myasthenia muscle score (decrease $\geq$ 10 points).

For each patient with a score deterioration, a clinical validation was then made with the medical team neurologist to determine if the shortage caused the deterioration, thus defining patients affected by the IVIg shortage context.

We examined the time course of functional scores in all patients (with or without IVIg treatment changes) to evaluate the link between severe supply shortage and clinical outcomes in our hospital's centre for neuromuscular diseases, using statistical analysis to evaluate the association between IVIg treatment changes and clinical impact.

2.3. *Statistical analysis*

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) software (V.23) using the paired Student *t*-test, the Wilcoxon signed-rank test, or the χ^2 test. A value of $P < 0.05$ was considered significant.

Fig. 1 illustrates this process.

3. Results

3.1. *Patient characteristics*

During our analysis period, 142 patients were included (median weight 76 ± 25 kg, median age 61.5 ± 15.2 years). Twenty patients were excluded from the first analysis due to incomplete data or death during the analysis period.

Among the 142 patients, 47 (33%) had CIDP, 40 (28%) had LSS, 39 (28%) had MMN, and 16 (11%) had myasthenia gravis.

Table 1 lists patient characteristics.

3.2. *Impact on treatment*

3.2.1. *Impact on patient care*

Out of 142 patients, 111 (78%) underwent a modification of their IVIg treatment. For the majority, changes were made at the height of the COVID-19 crisis; 45% of the modifications occurred in March 2018.

Some patients had more than one type of IVIg treatment change during this period. Globally, we noted 147 IVIg treatment changes related to IVIg shortage. IVIg treatment was delayed in 75 (68%) patients, IVIg dose was decreased in 41 (37%), and IVIg treatment was discontinued in 31 (28%). Out of the 111 patients whose IVIg treatment was modified, 77 (69%) had one type of IVIg treatment change and 32 (29%) had two types of IVIg treatment changes; two patients (2%) had three types of IVIg treatment changes (first delay, then dose reduction, and finally complete discontinuation).

Table 2 provides the distribution of IVIg treatment changes by dysimmune neuromuscular disease.

All IVIg treatment interruptions were maintained for at least one year. Nine (30%) of the patients for whom IVIg treatment was discontinued, were switched to other treatments: plasma exchange (PE) for five (16%) patients; corticosteroid therapy for four (13%) patients.

Among the patients whose IVIg therapy was delayed, the modified IVIg treatment schedule was maintained in 21 (28%). Among those whose IVIg dose was decreased, the modified dose was maintained in 14 (35%).

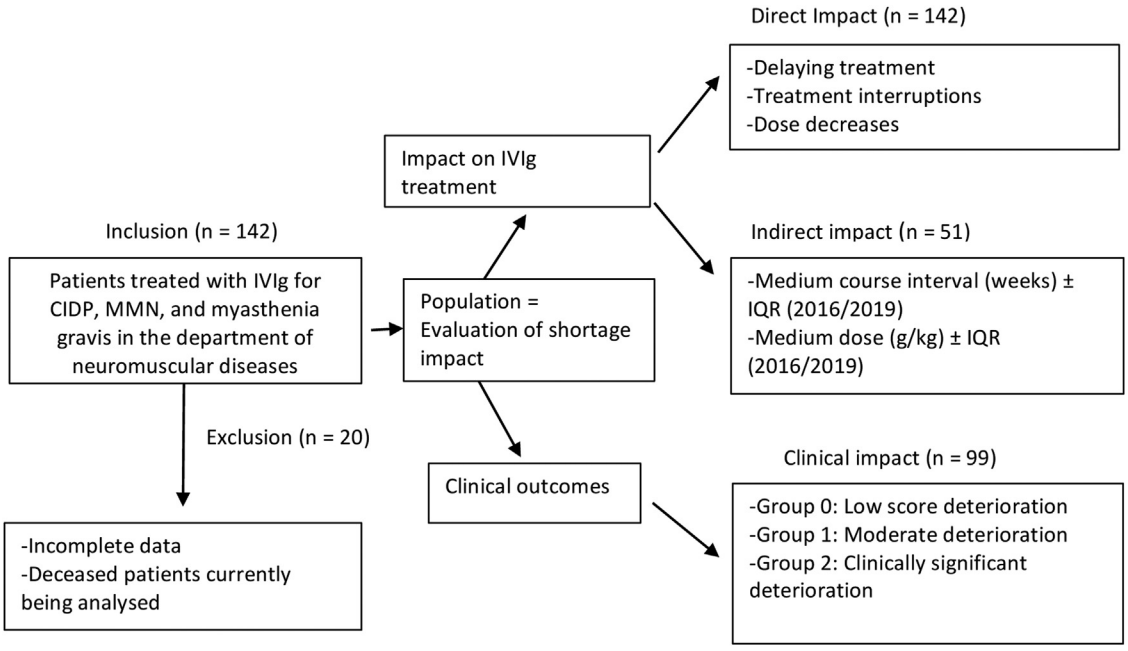

Fig. 1 – Study design.

Table 1 – Patient characteristics.

n = 142	Value
Age (years) ± IQR	61.5 ± 15.2 Range = 26–86
Weight (kg) ± IQR	76 ± 25 Range = 38.5–173
Sex ratio (H/F)	1.75
Disease distribution	
CIDP	47 (33%)
LSS	40 (28%)
MMN	39 (28%)
Myasthenia	16 (11%)
Median immunoglobulin dose (g/kg) per indication ± IQR	
CIDP	1.67 ± 0.44
LSS	1.71 ± 0.4
MMN	1.69 ± 0.53
Myasthenia	1.45 ± 0.6
Median interval between doses (weeks) per indication ± IQR	
CIDP	7.5 ± 4
LSS	8 ± 3
MMN	8.25 ± 3.5
Myasthenia	6 ± 2

CIDP: chronic inflammatory demyelinating polyneuropathy; LSS: Lewis and Sumner syndrome; MMN: multifocal motor neuropathy.

Table 3 notes the maintenance of IVIg treatment changes.

3.3. *Impact on medical practices*

The IVIg supply shortage changed medical practices indirectly. For this part of the analysis, 51 patients were included and 104 were excluded.

There was no significant difference in median dose before (i.e. 2016) versus after (i.e. 2019) the shortage for CIDP and LSS, but there was a significant decrease in IVIg median dose for MMN: 1.83 (range 1.13–2.62) g/kg in 2016 versus 1.69 (range 1.13–2.03) g/kg in 2019 ($P = 0.034$). For myasthenia gravis patients, there was a non-significant decrease in median dose: 1.73 (range 1.64–1.9) g/kg in 2016 versus 1.15 (range 1–1.62) g/kg in 2019 ($P = 0.423$).

Median delay between IVIg courses was significantly increased for CIDP and MMN patients. For CIDP patients, the median delay increased from 7 (range 4.5–13) to 7.5 (range 5–13) weeks ($P = 0.018$). For MMN patients, the median delay between IVIg courses increased from 7 (range 5–12) to 9 (range 6–13) weeks ($P = 0.011$). There was no significant difference in median delay between IVIg courses for myasthenia gravis and LSS patients.

Table 4 summarises all results related to medical practices.

3.4. *Clinical impact of IVIg treatment changes*

Out of the 111 patients who had IVIg treatment changes, 99 were retained for this analysis; 12 were excluded due to lack of data and incomplete patient medical records. The ONLS, RODS and myasthenia muscle scores of these 99 patients showed that score deterioration occurred in 58, including 31 with moderate or clinically significant deterioration as defined in Methods.

Among these 58 patients, 27 (47%) were classed in group 0 (low score deterioration), 21 (36%) in group 1 (moderate score deterioration), and 10 (17%) in group 2 (clinically significant deterioration). Eighteen (31%) patients had at least two types of IVIg treatment changes. For 17 (30%) patients, the clinical deterioration was directly linked to the shortage of IVIg. For six patients, only RODS deteriorated: these patients felt fatigue without an objective increase of deficit at clinical examination. Analysis of the functional score time course showed that IVIg treatment changes were significantly associated with clinical impact ($P = 0.001$).

Table 2 – Distribution of IVIg treatment changes by dysimmune neuromuscular disease.

	Total of cases	IVIg treatment delay	IVIg dose decrease	Discontinuation of IVIg treatment	Number of patients with at least one change	Total of changes
CIDP	47 (33%)	23 (49%)	12 (26%)	14 (30%)	35	49
LSS	40 (28%)	23 (58%)	13 (33%)	2 (0.1%)	29	38
MMN	39 (28%)	26 (67%)	10 (26%)	8 (21%)	33	44
Myasthenia	16 (11%)	3 (19%)	7 (44%)	6 (38%)	14	16
Total	142	75	41	31	111	147

Table 3 – Maintenance of IVIg treatment changes one year later after analysis period.

N = 147[a]	Modifications	Modifications not maintained
IVIg Dose decrease	41	27 (66 %) [b]
Delaying IVIg treatment	75	54 (72 %) [c]
Stopping IVIg treatment	31	0
Switch to plasma exchange	5	0
Switch to corticosteroids	4	0
Total	147 (45%)	81 (55%)

[a] We consider here 111 patients with modification corresponding to 147 modifications: 77 patients had 1 type of prescription changes, 32 patients had 2 types of prescription changes and 2 patients had 3 types.
[b] Including 10 Ig interruptions.
[c] Including 21 Ig interruptions.

Table 4 – Evolution of median doses and median intervals between two IV Ig treatments, before and after the shortage depending on dysimmune neuromuscular disease.

N = 51[a]	Median doses (g/kg) ± IQR		
	Before shortage-2016	After shortage-2019	P
CIDP (*n* = 12)	1.68 ± 0.35	1.67 ± 0.3	0.722
LSS (*n* = 16)	1.76 ± 0.25	1.72 ± 0.47	0.059
MMN (*n* = 19)	1.83 ± 0.31	1.69 ± 0.49	0.034
Myasthenia (*n* = 4)	1.73 ± 1	1.15 ± 0.5	0.423
N = 51[a]	Median intervals between treatments (weeks) ± IQR		
	Before shortage-2016	After shortage-2019	P
CIDP (*n* = 12)	7 ± 2	7.5 ± 4	0.011
LSS (*n* = 16)	7.5 ± 2	8 ± 2.5	0.167
MMN (*n* = 19)	7 ± 2	9 ± 3	0.018
Myasthenia (*n* = 4)	5 ± 0.2	5.25 ± 0.5	0.5

[a] Patients who were not monitored during the period under consideration are excluded.

Table 5 – Distribution of patients with deteriorating clinical score.

	Group 0 Low score deterioration	Group 1 Moderate deterioration	Group 2 Clinically significant deterioration	Total
Patients with two types of IVIg treatment changes at least*	7 (26%)	8 (38%)	3 (30%)	18
Patients with one type of IVIg treatment change*	20 (74%)	13 (62%)	7 (70%)	40
Total	27	21	10	58

Criteria: Group 0: Same ONLS score, RODS score decrease < 4 points, myasthenia muscle score decrease < 5 points; Group 1: ONLS score increase ≥ 1 point; RODS score decrease ≥ 4 and < 6 points; myasthenia muscle score decrease ≥ 5 and < 10 points; Group 2: ONLS score increase ≥ 2 points, RODS score decrease ≥ 6 points and myasthenia muscle score decrease ≥ 10 points.

* We consider here 3 types of IVIg treatment changes: IVIg treatment delay, discontinuation of IVIg treatment and IVIg dose decrease.

Table 5 summarises features observed in all patients with deteriorating clinical scores.

4. Discussion

Growing indications for Ig in recent years has led to an increase in consumption. At the same time, lack of raw materials has led to Ig shortage problems. This study allowed us to evaluate the impact of this situation on patient care in a French university centre.

One particular interest of this study is to note that the context of shortage led to essential re-evaluations of IVIg treatments, particularly concerning doses and delay between IVIg courses. Indeed, 111 patients (78%) experienced one or more types of change to their IVIg regimen.

This study allowed us to observe an increase of delays between IVIg courses for CIDP, LSS, MMN and myasthenic patients when IVIg shortage developed. However, depending on patient response, compliance with a longer delay between IVIg courses was not always possible. This need to maintain short intervals between courses corresponds to the IVIg-dependence phenomenon reported in several studies [9,10].

Dose reductions were made in order to rationalise prescriptions. Analysing dose changes since 2016, we noted that myasthenia patients were affected the most by dose reductions. In our centre, medical practices tended to come closer to dose levels recommended by the French drug safety agency (*Agence nationale de sécurité du medicament*, ANSM): 1 g/kg. Indeed, a 2005 study compared 1 g/kg to 2 g/kg in the treatment of myasthenia gravis and revealed no significant difference in efficacy between the two doses [13–15].

It is more difficult to reduce IVIg doses in patients with stabilised disease [16]. However, in a retrospective cohort study, gradual dose reduction was successful in 15 CIDP patients. Most patients began with an initial dose of 2 g/kg and were able to reduce this dose by about 63%. These results suggest that much smaller doses–at initiation or during

maintenance–could be effective, underlining the need for comparative tests [17].

The dose schedule and the dose adjustment strategy should both be adapted on a case-by-case basis, according to individual response. In the context of plasma shortage and regular lack of IVIg availability, dose reduction and wider treatment intervals lead to decreased IVIg consumption. An important issue in itself, wider treatment intervals could also involve improved patient quality-of-life and fewer hospitalisations.

This situation has also made it possible to discontinue certain IVIg treatments. IVIg treatments were stopped when patients were clinically stable, when complete symptom resolution was noted, or when there was no end-of-dose effect. As well, prescribers switched to corticosteroids, PE or an association of several immunomodulating treatments whenever possible in order to save Ig for patients who had no other alternatives, especially those with severe and chronic diseases [18–26]. Albeit, it is known that patients with LSS can get worse after corticosteroid treatment [27] and that MMN patients may have no other option than IVIg [28–31]. The choice of treatment therefore has to be made on a case-by-case basis.

About 16% of patients, particularly those with myasthenia gravis or CIDP were switched to PE. Nevertheless, the technical aspects and potential complications of PE require considerable technical skill implying non-negligible training time for the medical team. Moreover, many teams prefer IVIg treatments because PE is a relatively invasive treatment. In addition, each PE session requires hospitalisation for a few hours and four to five sessions, every other day, are necessary for optimal clinical results similar to those obtained with four sessions of IVIg infusions [32–34].

Our study has some limitations. It was conducted in a single centre and was retrospective. Missing data hampered the inclusion of many patients. For this study, we analysed RODS, MMN-RODS, ONLS and myasthenia muscle scores that are recognised as fundamental and robust. As well, it would have been interesting to have evaluated fatigue and quality-of-life scores that were unfortunately unavailable for this retrospective analysis.

French guidelines, which recommended use of Ig by priority according to indications, made it possible to re-evaluate treatment modalities, and thus to offer the most suitable treatment for each patient. This suggests that in the context of procurement constraints, a re-evaluation of the treatment regimen was conceivable for some patients. Such re-evaluations were effective in limiting the use of Ig in the context of national and international shortages. Nevertheless, this study demonstrated that treatment changes were not without side effects: we observed a deterioration of evaluation scores in about 31% of patients whose IVIg regimens were modified. This finding shows that IVIg treatment changes, directly related to IVIg shortages, had a negative impact on the clinical status of some patients. Indeed, the delay between IVIg courses is calculated according to the clinical deficit; an overly long interval can lead to disease flare-up, particularly for unstable patients. Moreover, for some diseases, IVIg appears to be the only treatment option. So, some patients without a real therapeutic alternative may have experienced therapeutic shortage. Moreover, maintenance treatments are not clearly defined; some practitioners reduce dose frequency and others dose level. Both techniques can induce deterioration. Practices need to be defined by scientific societies and justified in the literature.

A multidisciplinary consultation meeting is needed to initiate Ig treatment in CIDP and MMN patients. Furthermore, treatments for CIDP, MMN and myasthenia gravis cannot be initiated in France without prior consultation with a neuromuscular disease reference centre (*La filière de santé maladies neuromusculaires*, FILNEMUS). These meetings ensure optimal patient care and help regulate use of Ig. Regular evaluation of individual treatments is also part of this approach to improving appropriate use of Ig. In this context of procurement constraint, appropriate use of Ig has been a real public health issue and has required a change in practices and prescribing habits to reserve these products for warranted indications.

The interest of re-evaluating IVIg treatments remained significant in 2020. The COVID-19 pandemic has had a likely impact on global blood and plasma collection, on which Ig is dependent. This weakening of production due to a lack of raw material is likely to increase supply tensions in the next 6–10 months. The COVID-19 crisis heralds the beginning of a complicated period, and in this context, it can be expected that this type of study will develop more and more concerning drugs derived from blood or other products. As access to IVIg will be more difficult, other treatments should be considered to save plasma and Ig, for example rituximab or haematopoietic stem cell transplantation for second-line CIDP therapy should be discussed to spare IVIg [35].

5. Conclusion

Our study showed a significant number of changes in IVIg treatments directly related to the shortage of IVIg: delay between IVIg courses, IVIg dose reduction and discontinuation of IVIg treatment during the study period.

The context of shortage has made it necessary to re-evaluate important treatment options. For most patients, changes in IVIg treatments have been maintained.

At an international level, shortage is also the main issue: the Food and Drug Administration works in close collaboration with the producers to reduce as much as possible tension in the Ig supply situation [11].

Treatment re-evaluations will continue to be important because of the fragility of the post-COVID market. Rationalising and harmonising at an international level would be interesting in order to save plasma in this shortage context as well as to move on to better use of Ig.

Data availability statement

All de-identified data and related documentation from this study are available upon request to qualified researchers without limit of time, subject to a standard data sharing agreement.

Standard protocol approvals, registrations, and patient consents

This study was approved by the institutional research ethics board, Assistance Publique–Hôpitaux de Marseille, (PADS20-246).

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Disclosure of interest

The authors declare that they have no competing interest.

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