Short Communication

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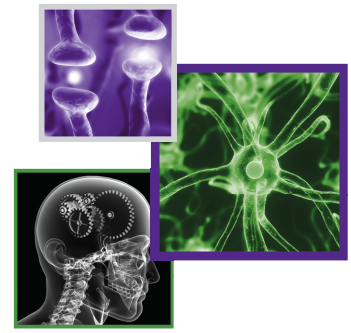
Neurodegenerative Disease Management



Octagam® for chronic inflammatory demyelinating polyneuropathy: results from three observational studies

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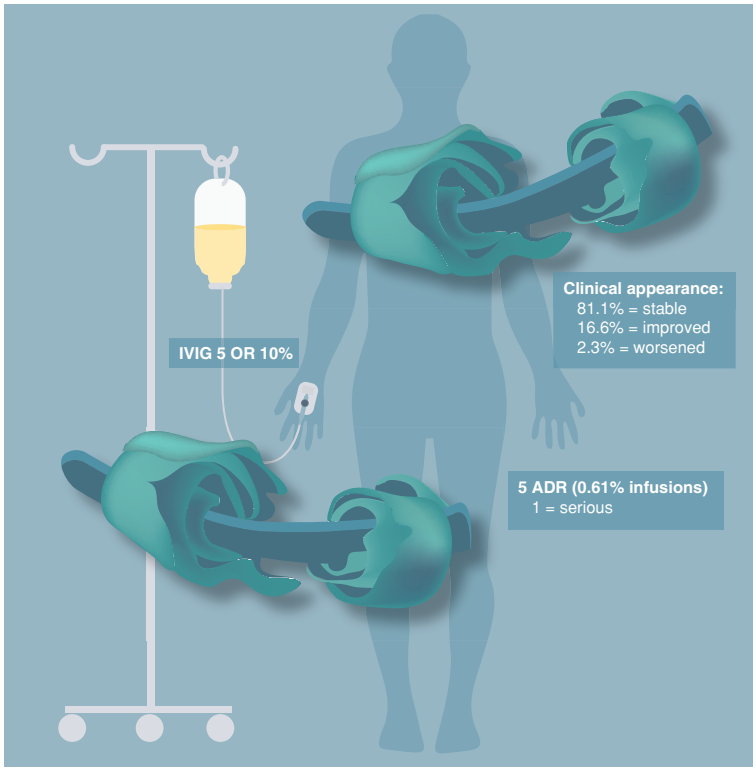
Practice points

- Octagam® was well-tolerated in patients with chronic inflammatory demyelinating polyneuropathy (CIDP).
- No thromboembolic events were reported in patients with CIDP.
- Stable clinical appearance of CIDP since last observation was reported by 81.1% of observations with Octagam and 16.6% of observations showed an improved clinical appearance.
- Octagam is safe and effective in the treatment of CIDP.

Aim: To present data from three studies of a Post-Authorization Safety Surveillance (PASS) program for the subset of patients receiving Octagam® 5% or 10% for chronic inflammatory demyelinating polyneuropathy (CIDP). **Methods:** Data on patients with CIDP treated with Octagam were analyzed to assess its safety and tolerability. **Results:** Of 2314 patients included in the studies, 58 patients (mean age: 64.6 years) received Octagam for CIDP, mean dose of which was 0.8 g/kg bodyweight/course. 81% of observations for clinical appearance since last observation were assessed as stable and 16.6% showed an improved clinical appearance with treatment. Adverse drug reactions were rare (<0.7% of infusions). **Conclusion:** Octagam was effective and well-tolerated in patients with CIDP.



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Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common chronic autoimmune neuropathy, with an estimated prevalence between 1 and 9 per 100,000 people [1–3]. It can cause temporary disability in the affected individuals and may eventually lead to permanent disability or death [1]. Besides corticosteroids and plasma exchange, intravenous immunoglobulin (IVIG) therapy is widely used as first-line treatment for CIDP [4,5] and certain IVIG brands are licensed in several countries. Octagam® 5% and Octagam 10% are liquid preparations of polyvalent human normal immunoglobulin for intravenous use. From June 2011 on, an additional and now mandatory chromatography step to remove activated factor XI was integrated in the standard preparation of raw material used to manufacture Octagam and it was deemed necessary to conduct Post-Authorization Safety Surveillance (PASS). This program comprised four studies and was designed to include at least 2000 patients, receiving at least 20,000 doses of Octagam 5% or 10%.

Here we present data from this PASS program for the subset of patients receiving Octagam for neurological indications (CIDP, Guillain–Barré syndrome [GBS], multifocal motor neuropathy [MMN], multiple sclerosis [MS] and myasthenia gravis [MG]), with a focus on those with CIDP as these patients often receive high doses of IVIG.

Materials & methods

The designs of the four PASS studies have been described in detail previously [6]. Briefly, the studies included both in- and out-patients who were treated with Octagam 5% or 10% for their medical condition during routine clinical practice. Of the four studies comprising the PASS program, three studies included patients receiving Octagam for neurological indications; two of these studies have been completed (ISRCTN58800347; the other not registered) and the third study is ongoing (ClinicalTrials.gov identifier NCT02303093; ISRCTN02245668; Table 1).

All three studies were open, multicenter, non-interventional, single-arm and noncontrolled. The dosage and duration of treatment depended on the type and severity of the disease and the patient's clinical condition. Data from these studies were documented by the physicians with the help of detailed electronic or paper case report forms, and all adverse drug reactions (ADRs), defined as any noxious and unintended response to the observational drug, meaning that a causal relationship between the observational drug and an adverse event is at least a reasonable possibility, were identified and reported as postmarketing safety data. For collecting data on the efficacy of Octagam in neurological indications, the investigators were asked to rate the development of the clinical appearance of the disease since the last visit as either 'improved', 'not changed' or 'deteriorated' since last infusion visit, while at the study close-out visit they were asked to assess the influence of Octagam treatment on the course of the disease (either 'beneficial', 'unchanged' or 'unfavorable').

Statistical analysis

Descriptive statistical analysis was used for all the study variables. The variables were summarized as mean, median, standard deviation and minimum and maximum, and two-sided 95% confidence intervals were included, wherever necessary. Statistical analysis of the data was performed using SAS software version 9.3.

Ethics

Where required by national regulations, the study protocol was reviewed and approved by each study site's Independent Ethics Committee before the start of the study and patients provided written informed consent for the collection of data prior to study entry.

Results

The three studies included a total of 2314 patients, of whom 260 (11.2%) were receiving treatment for neurological indications (Table 2). Of these 260 patients, 58 patients (22.3%) had CIDP (mean age: 64.6 years [range 18–88]) and received 813 infusions at a median course interval of 4.5 weeks, similar to MG, MS and MMN. Premedication was given only in 15.7% of the Octagam infusions in patients with CIDP. The mean dose per course for patients with CIDP was 0.8 g/kg bodyweight; the full dose was split over 2 or more days in 23.2% of courses. The mean

Table 1. Design of the three non-interventional Phase IV studies.

Study ID (registration)	Study design	Country	Octagam® strength	Study start and end dates	Period for integrated analysis (number of patients)
Study 1 (ISRCTN58800347)	OL, MC, NIS, one-arm, noncontrolled	Germany	10%	September 2008–December 2013	June 2011–November 2013 (803)
Study 2 (not registered)	OL, MC, NIS, one-arm, noncontrolled	Germany	5%	February 1995–December 2013	June 2011–March 2013 (1220)
Study 3 (ISRCTN02245668, NCT02303093)	OL, MC, NIS, one-arm, noncontrolled	Austria, Canada, France, Spain, UK	5% and 10%	August 2011–ongoing	August 2011–March 2014 (291)

MC: Multicenter; NIS: Noninterventional study; OL: Open label.

Table 2. Number of infusions and patients in each of the three studies that enrolled patients with neurological disorders.

	All studies, n (%)	Study 1 Octagam® 5%, n (%)	Study 2 Octagam® 10%, n (%)	Study 3 Octagam® 5% + 10%, n (%)
Number of infusions				
Total patients	21,535	11,164	8406	1965
Patients with any neurological indication	3374 (16)	1156 (10)	1574 (19)	644 (33)
Patients with CIDP	813 (24)	270 (23)	239 (15)	304 (47)
Patients with GBS	32 (1)	0 (0)	0 (0)	32 (5)
Patients with MMN	432 (13)	0 (0)	370 (24)	62 (10)
Patients with MS	2001 (59)	875 (76)	934 (59)	192 (30)
Patients with MG	96 (3)	11 (1)	31 (2)	54 (8)
Number of patients				
Total patients	2314	1220	803	291
Patients with any neurological indication	260 (11)	87 (7)	104 (13)	69 (24)
Patients with CIDP	58 (22)	11 (13)	21 (20)	26 (38)
Patients with GBS	6 (2)	0 (0)	0 (0)	6 (9)
Patients with MMN	17 (7)	0 (0)	6 (6)	11 (16)
Patients with MS	163 (63)	73 (84)	74 (71)	16 (23)
Patients with MG	16 (6)	3 (3)	3 (3)	10 (14)

CIDP: Chronic inflammatory demyelinating polyneuropathy; GBS: Guillain–Barré syndrome; MG: Myasthenia gravis; MMN: Multifocal motor neuropathy; MS: Multiple sclerosis.

dose per single infusion per day was 0.3 g/kg bodyweight. For the other neurologic indications, the dose ranged from 0.2 (for MS, 2001 infusions) to 1.4 g/kg bodyweight (for GBS, 32 infusions at a median course interval of 1.6 weeks), with a dose of 1.1 g/kg for MMN (432 infusions) and MG (96 infusions).

Efficacy

Of the 58 CIDP patients treated with Octagam, the development of clinical appearance since last observation (mean: every 9.7 months) was assessed in 41 patients by their treating physicians. The majority of observations (142/175; 81.1%) assessed the patients as stable and 16.6% (29/175) of observations showed an improved clinical appearance. Only 2.3% (4/175) of the observation periods resulted in deteriorations. Ten patients with MMN had 79 observations; 48 (60.8%) had improved, 29 (36.7%) did not change and two (2.5%) deteriorated. Of the 409 observations in 89 MS patients, 96 (21.8%) improved, 308 (75.3%) did not change and five (1.2%) deteriorated. In two studies that included 28 CIDP patients, physicians were asked at the end of an individual observation to assess the influence of Octagam on the course of the disease: physicians rated the influence as beneficial and as unchanged in 14 (50%) patients each.

Safety

Of the 3374 infusions received by patients with a neurological disorder, 15 (0.44% of infusions) were associated with an ADR. Of those, three were serious. A case was rated as serious if the patient needed to be hospitalized, or hospitalization was prolonged, the patient died, the event was life-threatening, resulted in persistent or significant

disability or caused congenital anomaly/birth defect. One thromboembolic event (TEE) case was reported among neurologic patients (one patient with MS). Among CIDP patients, five ADRs were reported (0.61% of infusions in this cohort) and only one was serious.

Discussion

In the present study, data from the subset of patients from the PASS program using higher doses of Octagam for the treatment of neurological disorders were evaluated for safety and tolerability. The results of the analysis showed that there was improved clinical appearance with Octagam treatment since last observation in 16.6% of infusions. Premedication was not needed in 84.3% of patients with CIDP, and ADRs were reported in 0.44% of infusions with neurological disorders (0.61% of CIDP patients). Overall, the treatment was well-tolerated in this subset of patients receiving Octagam for neurological indications, in particular for CIDP, and these results are consistent with data for the overall patient population [6].

The beneficial effects of IVIG in the treatment of CIDP are reported in several studies [3,7–8]. A randomized, double-blind, placebo-controlled, cross-over study in 117 patients with CIDP demonstrated a favorable short- and long-term response with IVIG treatment [9]. Other studies highlight the efficacy of IVIG over prednisolone in the treatment of CIDP [10,11], and a randomized-controlled study provided supporting evidence favoring the use of IVIG in the initial treatment of CIDP [12]. The data from this analysis add to the growing body of evidence supporting a beneficial role of IVIG in 97.7% of the patients with CIDP that improved, or at least remained stable, under Octagam treatment [13,14].

TEEs have been reported to be associated with the use of Octagam [15]. This was due to the presence of activated factor XI in clinically relevant concentrations in some Octagam batches, which was rectified by modifications in the manufacturing process to remove the activated factor XI [16]. The results of the analysis of data from the complete PASS program revealed a total rate of TEEs per infusion of 0.014% (three per 21,780 infusions). In two of these cases (one patient with secondary immunodeficiency and one with polymyositis), TEEs were assessed as unlikely related to the administration of Octagam, and in one, the causal relationship was assessed as possible. The latter TEE case was the only patient affected by a neurological disorder; it occurred in a patient with MS and cardiovascular risk factors. This shows that these events were effectively eliminated with the use of Octagam after modifications in the manufacturing process [6].

The main limitation of the study is the small number of patients with CIDP included in the population. Also, most of the patients were Caucasian, which may have introduced bias in the results.

Conclusion

Octagam was well-tolerated in patients with neurological disorders and can be effectively used in the treatment of CIDP.

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Ethical conduct of research

The author states that where required by national regulations, the study protocol was reviewed and approved by each study site's Independent Ethics Committee before the start of the study and patients provided written informed consent for the collection of data prior to study entry.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Lunn MP, Manji H, Choudhary PP, Hughes RA, Thomas PK. Chronic inflammatory demyelinating polyradiculoneuropathy: a prevalence study in south east England. *J. Neurol. Neurosurg. Psychiatry* 66(5), 677–680 (1999).

• **A prevalence study based on a large population of >14 million in south-east England that resulted in a prevalence of one per 100,000 that is usually given as the lower range for chronic inflammatory demyelinating polyneuropathy (CIDP).**

2. Chio A, Cocito D, Bottacchi E *et al.* Idiopathic chronic inflammatory demyelinating polyneuropathy: an epidemiological study in Italy. *J. Neurol. Neurosurg. Psychiatry* 78(12), 1349–1353 (2007).

• **This epidemiological study in a population >4.3 million in Piemonte and Val d'Aosta resulted in higher prevalence rate of CIDP (3.6 per 100,000) based on the definite, probable and possible criteria for CIDP published by the American Academy of Neurology in 1991.**

3. Eftimov F, Winer JB, Vermeulen M, De Haan R, Van Schaik IN. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst. Rev.* 12, CD001797 (2013).

• **This updated Cochrane report includes all important randomized and also long-term clinical trials of intravenous immunoglobulin (IVIG) products compared with placebo, plasma exchange, prednisolone or intravenous methylprednisolone. It concludes that compared with placebo, IVIG improves disability for at least 2–6 weeks with an NNTB (calculated numbers needed to treat for an additional beneficial effect) of only three.**

4. Donofrio PD, Berger A, Brannagan TH 3rd *et al.* Consensus statement: the use of intravenous immunoglobulin in the treatment of neuromuscular conditions report of the AANEM ad hoc committee. *Muscle Nerve* 40(5), 890–900 (2009).

5. Feasby T, Banwell B, Benstead T *et al.* Guidelines on the use of intravenous immune globulin for neurologic conditions. *Transfus. Med. Rev.* 21(2 Suppl. 1), S57–S107 (2007).

6. Frenzel W, Wietek S, Svae TE, Debes A, Svorc D. Tolerability and safety of Octagam® (IVIG): a postauthorization safety analysis of four noninterventional Phase IV trials. *Int. J. Clin. Pharmacol. Ther.* 54(11), 847–855 (2016).

7. Rajabally YA. Long-term immunoglobulin therapy for chronic inflammatory demyelinating polyradiculoneuropathy. *Muscle Nerve* 51(5), 657–661 (2015).

8. Hahn AF, Bolton CF, Zochodne D, Feasby TE. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy. A double-blind, placebo-controlled, cross-over study. *Brain* 119(Pt 4), 1067–1077 (1996).

9. Hughes RA, Donofrio P, Bril V *et al.* Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomized placebo-controlled trial. *Lancet Neurol.* 7(2), 136–144 (2008).

•• **The first long-term randomized clinical trial comparing IVIG treatment with placebo for up to 48 weeks. The positive results led to the approval of the first IVIG brand in CIDP.**

10. Hughes R, Bensa S, Willison H *et al.* Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann. Neurol.* 50(2), 195–201 (2001).

11. Nobile-Orazio E, Cocito D, Jann S *et al.* Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomized controlled trial. *Lancet Neurol.* 11(6), 493–502 (2012).

• **The authors compared efficacy and tolerability of IVIG versus intravenous methylprednisolone over 6 months, thus, being one of the very few long-term studies of CIDP treatment. IVIG was less frequently discontinued than intravenous methylprednisolone.**

12. Mendell JR, Barohn RJ, Freimer ML *et al.* Randomized controlled trial of IVIG in untreated chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology* 56(4), 445–449 (2001).

13. Latov N. Diagnosis and treatment of chronic acquired demyelinating polyneuropathies. *Nat. Rev. Neurol.* 10(8), 435–446 (2014).

14. Querol L, Rojas-Garcia R, Casasnovas C *et al.* Long-term outcome in chronic inflammatory demyelinating polyneuropathy patients treated with intravenous immunoglobulin: a retrospective study. *Muscle Nerve* 48(6), 870–876 (2013).

15. European Medicines Agency. Questions and answers on the suspension of the marketing authorisations for Octagam (human normal immunoglobulin 5% and 10%); outcome of a procedure under Article 107 of Directive 2001/83/EC (EMA-588737–2010) (2011). www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Octagam_107/WC500097044.pdf

16. European Medicines Agency. European Medicines Agency recommends lifting of suspension of Octagam (2011). www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/2004/news_detail_001242.jsp&mid=WC001240b001201ac058004d001245c001241