



## Frequency and time to relapse after discontinuing 6-month therapy with IVIg or pulsed methylprednisolone in CIDP

This is the peer reviewed version of the following article:

*Original:*

Nobile Orazio, E., Cocito, D., Jann, S., Uncini, A., Messina, P., Antonini, G., et al. (2015). Frequency and time to relapse after discontinuing 6-month therapy with IVIg or pulsed methylprednisolone in CIDP. JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY, 86(7), 729-734 [10.1136/jnnp-2013-307515].

*Availability:*

This version is available <http://hdl.handle.net/11365/974609> since 2017-05-16T18:56:56Z

*Published:*

DOI:10.1136/jnnp-2013-307515

*Terms of use:*

Open Access

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. Works made available under a Creative Commons license can be used according to the terms and conditions of said license.

For all terms of use and more information see the publisher's website.

(Article begins on next page)

Frequency and time to relapse after discontinuing 6-month therapy with IVIg or pulsed methylprednisolone in CIDP

Eduardo Nobile-Orazio, MD, PhD,<sup>1</sup> Dario Cocito, MD,<sup>2</sup> Stefano Jann, MD,<sup>3</sup> Antonino Uncini, MD,<sup>4</sup> Paolo Messina, MSc,<sup>5</sup> Giovanni Antonini, MD,<sup>6</sup> Raffaella Fazio, MD,<sup>7</sup> Francesca Gallia, MD,<sup>1</sup> Angelo Schenone, MD,<sup>8</sup> Ada Francia, MD,<sup>9</sup> Davide Pareyson, MD,<sup>10</sup> Lucio Santoro, MD,<sup>11</sup> Stefano Tamburin, MD,<sup>12</sup> Guido Cavaletti, MD,<sup>13</sup> Fabio Giannini, MD,<sup>14</sup> Mario Sabatelli, MD,<sup>15</sup> Ettore Beghi, MD,<sup>5</sup> for the IMC Trial Group\*

<sup>1</sup> 2nd Neurology, Department of Medical Biotechnology and Translational Medicine, Milan University, Humanitas Clinical and Research Center, Rozzano, Milan, <sup>2</sup> Department of Neuroscience, A.O. Città della Salute e della Scienza di Torino, Turin, <sup>3</sup> Department of Neuroscience, Niguarda Ca' Granda Hospital, Milan, <sup>4</sup> Department of Neuroscience and Imaging, University "G. D'Annunzio", SS Annunziata Hospital, Chieti, <sup>5</sup> Laboratory of Neurological Disorders, IRCCS Mario Negri Institute, Milan, <sup>6</sup> Department of Neuroscience, Mental Health and Sensory Organs, Rome University "Sapienza", Sant'Andrea Hospital, Rome, <sup>7</sup> Department of Neurology, San Raffaele Scientific Institute, INSPE, Milan, <sup>8</sup> Department of Neuroscience, Ophthalmology and Genetics, Genoa University, San Martino Hospital, Genoa, <sup>9</sup> Department of Neurology and Psychiatry, Umberto I° Policlinico, Rome, <sup>10</sup> Central and Peripheral Degenerative Neuropathy Unit, IRCCS Foundation, Carlo Besta Neurological Institute, Milan, <sup>11</sup> Department of Neurosciences, Reproductive Sciences and Odontostomatology, Federico II° University, Naples, <sup>12</sup> Department of Neurological and Movement Sciences, Verona University, Policlinico G.B. Rossi, Verona, <sup>13</sup> Department of Surgery and Translational Medicine, Milan Bicocca University, San Gerardo Hospital, Monza, <sup>14</sup> Department of Medical and Surgical Sciences, and Neurosciences, Siena University, Policlinico Le Scotte, Siena, <sup>15</sup> Department of Neurology, Catholic University, Policlinico Gemelli, Rome, Italy.

\* Members listed at the end of the report

Address correspondence to:

E. Nobile-Orazio, M.D., Ph.D.

Department of Medical Biotechnology and Translational Medicine, University of Milan

2<sup>nd</sup> Neurology, Humanitas Clinical and Research Center,

Via Manzoni 56, 20089, Rozzano, Milan, ITALY

Tel. No: 39+02.8224.2209; Fax No: 39+02.8224.2298

E-mail: [eduardo.nobile@unimi.it](mailto:eduardo.nobile@unimi.it)

**Key words:** Chronic inflammatory demyelinating polyradiculoneuropathy; CIDP; IVIg; corticosteroids; Methylprednisolone; Follow-up.

**Word count: 2978**

**Abstract: 257**

**Number of References: 27**

## **Abstract**

**Background:** We reported that 6-month therapy with intravenous immunoglobulin (IVIg) was more frequently effective or tolerated than methylprednisolone (IVMP) in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). We now retrospectively compared the proportion of patients who eventually worsened after discontinuing therapy and the median time to clinical worsening.

**Methods.** By march 2013, data were available from 41 of the 45 patients completing the trial with a median follow-up after therapy discontinuation of 42 months (range 1-60). Three patients withdrew during the original study and one failed to respond to both therapies. No patient received a diagnosis alternative to CIDP during the follow-up.

**Results.** Twenty-eight of the 32 patients treated with IVIg (as primary or secondary therapy after failing to respond to IVMP) improved after therapy (87.5%) as compared to 13 of the 24 patients treated with IVMP as primary or secondary therapy (54.2%). After a median follow-up of 42 months (range 1-57), 24 out of 28 patients responsive to IVIg (85.7%) worsened after therapy discontinuation. The same occurred to 10 out of 13 patients (76.9%) responsive to IVMP (p: 0.659) after a median follow-up of 43 months (range 7-60). Worsening occurred 1-24 months (median 4.5) after IVIg discontinuation and 1-31 months (median 14) after IVMP discontinuation (p: 0.0126).

**Conclusions.** A similarly high proportion of patients treated with IVIg or IVMP eventually relapse after therapy discontinuation but the median time to relapse was significantly longer after IVMP than IVIg. This difference may help to balance the more frequent response to IVIg than to IVMP in patients with CIDP.

## **Introduction**

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare and often disabling chronic progressive or relapsing neuropathy.[1,2] Several data point to an immune pathogenesis of CIDP[3] including the improvement observed in most patients after therapy with corticosteroids, plasma exchange and high-dose intravenous immunoglobulin (IVIg).[4-7] Two randomised controlled trials (RCTs) showed a comparable short-term efficacy of IVIg and oral corticosteroids[8] and of IVIg and plasma exchange,[9] while a recent RCT (the IMC study), showed that six-month therapy with IVIg was more frequently effective and tolerated than treatment with intravenous methylprednisolone (IVMP).[10] Little is known on the long-term effect of these therapies and on the duration of their effect after discontinuation. In two RCTs, discontinuation of IVIg after six-month therapy was followed by clinical deterioration within six months in approximately half of the patients.[11, 12] In one[11] of these studies, therapy continuation was more effective than placebo up to 48 weeks. The follow-up extension[13] of the PREDICT study[14] showed that the median time to relapse after discontinuation of six-month therapy ranged from 11 months for oral prednisolone to 17.5 months for pulsed high-dose dexamethasone. In the IMC study[10] a significantly higher proportion of patients relapsed and required further therapy within six months after IVIg ( 38.1%) than IVMP discontinuation (0/10). We have now extended the follow-up of this study to compare the proportion of patients who eventually deteriorated and resumed therapy during the follow-up and the time to clinical deterioration after discontinuing six-month therapy with IVIg or IVMP.

## **Patients**

We retrospectively reviewed the follow-up of the patients included in the IMC study after the last scheduled visit of the trial, six-month after therapy discontinuation. Of the 45 patients included in the IMC study, 42 patients were available at follow-up since three patients (all on IVMP) had retired from the original study for adverse events (1) or voluntary withdrawal (2) and refused further therapy within the trial.[10] In the original study, patients who had failed to respond to one therapy were blindly treated for six-months with the alternative therapy. We included these patients in the analysis of the long-term efficacy of the therapies. They included 8 patients treated with IVIg after failing to IVMP and three patients treated with IVMP after failing to IVIg.

According to the original protocol, all the patients were included if they were at least 18 years old, had definite typical CIDP according to the EFNS/PNS criteria,[7] had some disability either in the overall neuropathy limitation scale (ONLS)[15] (scoring 2 or more) or in the Rankin scale[16] (scoring 2 or more), and were in active or stationary phase but not in remission. Patients were excluded if they had atypical CIDP,[7] a diagnosis of multifocal motor neuropathy, or other underlying causes including diabetes and IgM monoclonal gammopathy with anti-MAG or anti-sulfatide IgM. Patients were also excluded if they had concurrent medical disorders preventing treatment or assessment or contraindications to steroid or IVIg therapy. Patients with a documented lack of response to a previous course of an effective dose of steroids or IVIg were also excluded. Patients received for four consecutive days either IVIg (IgVena, Kedrion SpA, Italy) at the daily dose of 0.5g/kg associated with intravenous steroid-placebo or daily IVMP 0.5 g in 250 ml of sodium chloride solution associated with IVIg-placebo. Each patient was treated at monthly intervals (28 days +/-3) for six months after which therapy was discontinued. Patients who had not improved by at least one point in the ONLS or Rankin score after the first two courses of therapy were allowed to shift to the alternative therapy. Similarly, patients not tolerating the first therapy or worsening by at least one point in the ONLS or Rankin score after the first therapy were shifted to the alternative therapy.

All patients gave written informed consent before inclusion in the original study that was registered under the EUDRACT code no. 2005-001136-76. The study was approved by the Ethic Committees of Humanitas Clinical and Research Center, Via Manzoni 56, 20089, Rozzano, Milan, Italy, and of the other participating centres who also approved the retrospective analysis of the follow-up of the patients.

## **Methods**

In this retrospective follow-up study, patients were not evaluated at fixed intervals but were usually assessed every one to two months and at any time they reported clinical worsening. Patients were considered to be deteriorated and therefore treated if they reported a clinical worsening that was objectively verified by the treating neurologist. This included a deterioration by at least one point in the ONLS or modified Rankin scale as we did in the original study[10] but also one point in the MRC sumscore[17] as far as this was consistent with the reported subjective worsening. No specific treatment was used at the time of deterioration as this was decided independently by the treating physician. Similarly, response to this treatment was not

analysed since the assessment and interval after therapy were not standardized among the different Centres. Data on side effects of treatments and other adverse events occurred during the follow-up were also collected. Treating neurologists were also enquired whether, at the time of last-follow, a diagnosis different from CIDP was made in any of the patients.

The main outcome of the study was the difference in the proportion of patients who deteriorated and resumed treatment after therapy discontinuation. Secondly we evaluated also the mean and median time from therapy discontinuation to clinical deterioration. We also evaluated the difference in the adverse events reported by patients and the proportion of patients who had diagnosis changed during the follow-up. We included in the study patients who had failed to respond to one therapy and who were subsequently blindly treated for six-months with the other therapy.

### **Statistical Analysis**

Differences between the two groups were assessed by the Fisher's exact test and Wilcoxon Mann Whitney test as appropriate. Time to relapse was compared between groups using the Kaplan-Meier survival curves, and curves were censored at 1, 2 and 3 years of follow-up. The Wilcoxon test was used to compare the Kaplan-Meier survival curves in order to account for non proportional hazards. Data were also analysed on an intention-to-treat (ITT) basis according to the original protocol only including the 10 patients who improved after the initial 6-months therapy with IVMP and the 21 patients who improved after the initial 6-months treatment with IVIg. All statistical analyses were performed with significance set at the 5% level and using 2-sided tests or 2-sided 95% confidence intervals (CIs). All the analyses were performed including patients who withdrew or died during the follow-up.

### **Results**

Overall, 32 patients had been treated with IVIg as first (24 patients) or second therapy (8 patients) and 24 with IVMP as first (21 patients) or second therapy (3 patients) (Figure 1). Twenty-eight of the 32 patients treated with IVIg (87.5%) had improved by at least one point in the ONLS or modified Rankin scale, as compared to 13 of the 24 patients (54.2%) treated with IVMP as first (21) or second (3) therapy (Table). One patient failed to respond to IVMP and IVIg and died three months after the trial for the

relentless progression of the neuropathy. By March 2013, follow-up data were available from 41 patients who had improved after six-month therapy with IVIg (28 patients) or IVMP (13 patients) with a median follow-up after therapy discontinuation of 42 months (range 1-60). Two of these patients had been lost during the follow-up for voluntary withdrawal 1 month (treated first with IVMP, then with IVIg) and 7 months (treated with IVMP) after the last scheduled therapy while two patients died.[10] One of them had a cardiac arrest one month after the last IVIg course and two days after the six-month visit of the original study. The patient had hypertension and cardiovascular risk factors and was treated with oral anticoagulants, but a possible relation to the assigned treatment could not be excluded. The second received six courses of IVIg after having worsened after one course of IVMP. Two months after the last IVIg course and one month after the six-month visit he died for respiratory failure. Even if we only had a few data since the patient died when he was abroad, we think it was unlikely that death was treatment related but we cannot exclude that it was caused by disease progression. All patients who withdrew or died during the follow-up were classified as deteriorated at the time of withdrawal or death.

The median follow-up after therapy discontinuation was similar in patients treated with IVIg (median 42 months; range 1-57) or IVMP (median 43 months; range 7-60 months) ( $p = 0.765$ ). During this time no patient received a diagnosis alternative to CIDP. Twenty-four of the 28 patients responsive to IVIg (85.7%) worsened after therapy discontinuation (21/25 excluding patients who had deceased or withdrew from the study, 84%). The same occurred to 10 of 13 patients (76.9%) responsive to IVMP ( $p = 0.659$ )(9/12 excluding patients who withdrew, 75%). Clinical deterioration occurred 1 to 24 months (median 4.5) after IVIg discontinuation and 1-31 months (median 14) after IVMP discontinuation ( $p = 0.0126$ ). Kaplan-Meier survival curves of the between groups time to relapse censored at 1, 2 and 3 years of follow-up (Figure 2) reported Wilcoxon  $p$ -values of 0.0139, 0.0272, 0.0278.

Similar results were observed in the patients who responded to their first therapy so did not shift to the alternative therapy. Seventeen of the 21 patients responsive to 6-months therapy with IVIg (80.9%) worsened after therapy discontinuation after a median follow-up of 42 months (range 1-57). The same occurred in eight of the 10 patients responsive to IVMP (80%)( $P = 1.0$ ) (median follow-up 43.5 months; range 7-60). Clinical deterioration occurred 1 to 24 months (median 6) after IVIg discontinuation and 7-16 months (median 12) after IVMP discontinuation ( $p = 0.0295$ ). In this group of patients Kaplan-Meier



survival curves of the between groups time to relapse censored at 1, 2 and 3 years of follow-up yielded Wilcoxon p-values of 0.0339, 0.0396 and 0.0396. A similar tendency was observed among the patients who responded to the second therapy. All the seven patients who responded to IVIg after failing to respond to IVMP, worsened (5 patients), withdrew (2 patients) or died (one patient) 1 to 9 months (median 2 months) during a follow-up of 1-53 months (median 43) after therapy discontinuation. The same occurred during a follow-up of 32-50 months (median 42), to two of the three patients (66.6%) who responded to IVMP after failing to respond to IVIg and who worsened after 1 and 31 months.

We also analyzed the data on an intention to treat basis of the originally randomized patients to steroids or IVIg including the data from those who had failed to respond to the first therapy and were shifted to the alternative therapy. Of the 21 patients randomized to steroids, 10 patients (47.5%) had improved by the second month of therapy with steroids as did seven of the eight patient shifted to IVIg. A total of 17/21 (80.9%) patients in this group improved with a median time to improvement of 3 months. Of the 24 patients randomized to IVIg, 21 (87.5%) improved by the second month of therapy with IVIg as did the three patients who shifted to steroid. A total of 24/24 (100%) patients improved ( $p=0.212$  compared to the steroid group) with a median time to improvement of 2 months. After a median follow-up of 43 months (range 1-60 months) after therapy discontinuation, 15 of the 17 patients (88.2%) improved in the steroid group, relapsed (12 patients), withdrew (2 patients) or died (1 patient), 1-16 months (median 8 months) after therapy discontinuation. The same occurred in 19 of the 24 patients (79.1%) improved in the IVIg group ( $p=0.4216$  compared to steroid) after a median follow-up of 42 months (range 7-57 months). These patients relapsed (18 patients) or died (1 patient) 1-31 months (median 6.5 months) ( $p=0.858$  compared to steroids) after therapy discontinuation.

Of the four patients who voluntarily withdrew or died during the follow-up, one only received IVIg (a patient who died because of cardiac arrest), one only received IVMP (a patient who withdrew) and two received IVIg after failing to respond to steroids (one retired and one died of respiratory failure). Including the data from the IMC trial,[10] four out of 24 patients (16.7%) withdrew (3) or had serious adverse events (1) during IVMP or after its discontinuation compared to three out of 32 patients (9.4%) who withdrew (1) or died (2) during or after IVIg ( $p=0.4465$ ). Of the 30 patients who worsened after therapy discontinuation and who were available at follow-up, 20 were treated at the time of deterioration with intravenous (19) or

subcutaneous immunoglobulin (1) and 10 with oral steroids (5) or IVMP (5). Two of them had a non fatal myocardial infarction including one treated with IVIg and one with oral steroids.

## **Discussion**

This retrospective analysis of the follow-up of CIDP patients enrolled in the IMC study[10] extended the data observed at 6 months after therapy discontinuation showing that, when efficacious and tolerated, IVMP has a longer median efficacy (14 months) than IVIg (4.5 months) after therapy discontinuation. The proportion of patients who eventually deteriorated was however similar after IVIg (85.7%) and IVMP (76.9%) during the same follow-up (median time 42 for IVIg and 43 months for IVMP). Similar data were obtained when the analysis was restricted to the patients responsive to the initial treatment in the IMC study. No difference was seen on the intention to treat analysis of the patient originally randomized to IVMP or IVIg. This probably reflects the fact that the majority of patients who had failed to respond to the first therapy were shifted after one to two courses of the initial regimen to a six-month blinded treatment with the alternative therapy that might have influenced the follow-up of the patients more than the short initial therapy. This at least appears by the rate of response and time of worsening after therapy discontinuation in the patients who responded to the second therapy. Starting with IVMP and switching to IVIg in case of no response, may be therefore economical advantageous compared to starting with IVIg but should be balanced with the more frequent initial response to IVIg (87.5%) than to IVMP (54.2%) that was confirmed in this study after the inclusion of patients who had failed to respond to the first therapy and who were blindly treated with the alternative therapy.

Despite the retrospective nature of this follow-up study, all the patients were originally included in a double-blind RCT, limiting the possible selection bias connected with the initial choice of treatment. The main limitation of the study is however the fact that, after the 6-month follow-up visit after therapy discontinuation, patients were not observed at fixed periods of time. The verification of subjective worsening might have therefore occurred with some difference in time from centre to centre. This discrepancy similarly applied however to all patients independently from the therapy used.

A similar difference in the prolonged efficacy of therapy after discontinuation can be derived from previous studies that analyzed the frequency of deterioration after therapy discontinuation. Two RCTs

showed that discontinuation of 6-month therapy with IVIg was followed by clinical deterioration in 45 % of the patients after 24 weeks[11] while 48% of the patients deteriorated within 16 weeks after discontinuing 16 weeks therapy with IVIg.[12] The extension of the PREDICT study[13] showed that the median time to relapse after therapy discontinuation was 11 months for oral prednisolone and 17.5 months for pulsed oral dexamethasone. The relatively shorter median time to deterioration (14 months) observed in our study compared to what observed in the group treated with pulsed dexamethasone (17.5 months) may possibly reflect the fact that we considered deteriorated patients in whom subjective worsening was confirmed by the loss of even one point in the MRC sumscore. A similar more prolonged efficacy of steroids than of IVIg can be assumed from two uncontrolled five year follow-up study of 38[18] and 70[19] patients with CIDP, in whom the possibility to stop treatment with complete remission tended to be more frequent in patients who responded to steroids.

The results of this study may have an impact on the choice of the initial treatment in patients with CIDP. The majority of patients with CIDP requires prolonged therapy facing the inconveniences of repeated infusions and elevated costs related to IVIg or the side effects often associated with the prolonged use of corticosteroids.[20] Several immunosuppressive agents have been used in CIDP[21] to improve the effect of therapy or to reduce its cost or side-effects. None of these therapies have been however confirmed effective in RCT.[12, 22-24] In our study more patients treated with IVMP (16.7%) than IVIg (9.4%) voluntarily withdrew, had adverse events or retired during follow-up possibly reflecting a lower “appeal” for IVMP. This difference was not however significant. On the other hand, both patients who deceased did so after discontinuing IVIg even if the relation with the therapy remains unclear. The lack of differences in adverse events between patients treated with IVMP and IVIg might reflect the relatively short period of treatment with steroids (6 months). It is also possible however that pulsed monthly therapy with steroids might be better tolerated than oral steroids as suggested by some previous studies showing that pulsed corticosteroids therapy in CIDP is associated with less adverse events than daily oral steroids.[25-27]

In conclusion, this study shows that a similarly high proportion of patients with CIDP eventually relapsed after discontinuing six-month therapy with IVIg or IVMP. The median time to relapse was however significantly longer after discontinuing IVMP (14 months) than IVIg (4.5 months) confirming that, when effective, IVMP has a longer beneficial effect in CIDP compared to IVIg. This difference together with the

lower cost of IVMP than of IVIg may balance the more frequent initial efficacy of IVIg than of IVMP in CIDP.

Table

Follow-up of the patients discontinuing 6-month therapy with IVIg or IVMP including patients shifted to the alternative therapy after failure of the first drug

Patients treated	IVIg (n=32)	IVMP (n=24)	p-value
Improved, <i>n (%)</i>	28 (87.5)	13 (54.2)	
Median follow-up of improved patients, months ( <i>range</i> )	42 (1-57)	43 (7-60)	0.765
Improved patients worsened during the follow-up,* <i>n (%)</i>	24/28 (85.7)	10/13 (76.9)	0.659
Median time (months) to deterioration, ( <i>range</i> )	4.5 (1-24)	14 (1-31)	0.0126

\* Includes two patients who retired 1 and 7 months and two who died 1 and 2 months after the last scheduled therapy (3 after IVIg, 1 after IVMP)

## **Competing Interests**

- Eduardo Nobile-Orazio reports personal compensation for serving in the Steering or Advisory Board of Baxter, Italy, CSL Behring, Italy, Kedrion, Italy, and Novartis, Switzerland. He received honoraria for lecturing from Baxter, CSL Behring, Grifols, Spain, and Kedrion and travel supports for Scientific Meetings from Baxter and Kedrion. All compensations and supports are outside the submitted work.
- Dario Cocito and Raffella Fazio received honoraria for consulting from CSL Behring and Baxter and travel supports for Scientific Meetings from Kedrion, Italy, outside the submitted work.
- Stefano Jann, Angelo Schenone, Fabio Giannini and Mario Sabatelli have nothing to disclose.
- Lucio Santoro received travel supports for Scientific Meetings from Grifols, and Kedrion, Italy, outside the submitted work
- Antonino Uncini, Ada Francia, Davide Pareyson and Guido Cavaletti, received travel supports for Scientific Meetings from Kedrion, Italy, outside the submitted work
- Paolo Messina reports grants from Italian Drug Agency, grants from Italian Ministry of Health, grants from EISAI, grants from Lombardy Region, outside the submitted work;
- Francesca Gallia received travel support for Scientific Meetings from CSL-Behring and Kedrion, Italy, outside the submitted work.
- Giovanni Antonini received travel supports for Scientific Meetings from Baxter, CSL Behring, and Kedrion, Italy, outside the submitted work
- Stefano Tamburin received travel support for Scientific Meeting from Grifols, Italy, outside the submitted work
- Ettore Beghi served in the Advisory Board of Viropharm. He received honoraria for lecturing from UCB-Pharma and Viropharma. He received Research Grants from AIFA, Italy, American ALS Association, EISAI, GSK, Italian Ministry of health, UCB-Pharma. All compensation and supports are outside the submitted work.

## **Funding**

No fund was receive for this study.

## References

1. Hahn AF, Hartung H-P, Dyck PJ. Chronic inflammatory demyelinating polyradiculoneuropathy. In: Dyck PJ, Thomas PK, eds. *Peripheral Neuropathy*, 4th edn. Elsevier Saunders, Philadelphia, 2005:2221-2253.
2. Vallat J-M, Sommer C, Magy L. Chronic inflammatory demyelinating polyradiculoneuropathy: diagnostic and therapeutic challenges for a treatable condition. *Lancet Neurol* 2010;**9**:402-12
3. Hughes RAC, Allen D, Makowska A, Gregson NA. Pathogenesis of chronic inflammatory demyelinating polyradiculoneuropathy. *J Peripher Nerv Syst* 2006;**11**:30-46.
4. Eftimov F, Winer JB, Vermeulen M, et al. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 2009;**1**:CD001797.pub2.
5. Mehndiratta MM, Hughes RAC. Corticosteroids for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 2002;**1**:CD002062.
6. Mehndiratta MM, Hughes RAC, Agarwal P. Plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 2004;**3**:CD003906.pub2.
7. Joint Task Force of the EFNS and the PNS. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *J Peripher Nerv Syst* 2005; **10**:220-228.
8. Hughes RAC, Bensa S, Willison HJ, et al., and the Inflammatory Neuropathy Cause and Treatment (INCAT) group Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 2001;**50**:195-201
9. Dyck PJ, Litchy WJ, Kratz KM, et al. A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol* 1994;**36**:838-845.
10. Nobile-Orazio E, Cocito D, Jann S, et al. Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomised controlled trial. *Lancet Neurol* 2012;**11**:493-502.

11. 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* 2008;**7**:136-44.
12. Hughes RAC, Gorson KC, Cros D, et al. Intramuscular interferon beta-1a in chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology* 2010;**74**:651-657.
13. Eftimov F, Vermeulen M, van Doorn PA, et al. Long-term remission of CIDP after pulsed high-dose dexamethasone or short term prednisolone treatment. *Neurology* 2012; **78**:1079-1084.
14. van Schaik IN, Eftimov F, van Doorn PA, et al. Pulsed high-dose dexamethasone versus standard prednisolone treatment for chronic inflammatory demyelinating polyradiculoneuropathy (PREDICT study): a double-blind randomised controlled trial. *Lancet Neurol* 2010; **9**:245-253.
15. Graham RC, Hughes RA. A modified peripheral neuropathy scale: the overall neuropathy limitation scale. *J Neurol Neurosurg Psychiatry* 2006;**77**:973-76.
16. Bamford JM, Sandercock PA, Warlow CP, Slattey J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1989;**20**:828.
17. Kleyweg RP, van der Meché FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barré syndrome. *Muscle Nerve* 1991;**14**:1103-09.
18. Kuwabara S, Misawa S, Mori M, et al. Long term prognosis of chronic inflammatory demyelinating polyneuropathy: a 5 year follow-up of 38 cases. *J Neurolo Neurosurg Psychiatry* 2006;**77**:66-70.
19. Rabin M, Mutlu G, Stojkovic T, et al. Chronic inflammatory demyelinating polyradiculoneuropathy: search for factors associated with treatment dependence or successful withdrawal. *J Neurol Neurosurg Psychiatry* 2014;**85**:901-906.
20. Dukes MN. Meyler's side effects of drugs. Elsevier, New York; 1996:1193-1209
21. Mahdi-Rogers M, Swan AV, van Doorn PA, et al. Immunomodulatory treatment other than corticosteroids, immunoglobulin and plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst Rev* 2010;**11**:CD003280..
22. Dyck PJ, O'Brien P, Swanson C, et al. Combined azathioprine and prednisone in chronic inflammatory demyelinating polyneuropathy. *Neurology* 1995;**35**:1173-76



23. Hadden RDM, Sharrack B, Bensa S, et al. Randomized trial of interferon  $\beta$ -1a in chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology* 1999;**53**:57-61
24. RMC Trial Group. Pilot Randomised Controlled Trial of Methotrexate for Chronic Inflammatory Demyelinating Polyradiculoneuropathy (RMC Trial). *Lancet Neurol* 2009;**8**:158-164
25. Muley SA, Kelkar P, Parr GJ. Treatment of chronic inflammatory demyelinating polyneuropathy with pulsed oral steroids. *Arch Neurol* 2008;**65**:1460-1464.
26. Lopate G, Pestronk A, Al-Lozi M. Treatment of chronic inflammatory demyelinating polyneuropathy with high-dose intermittent intravenous methylprednisolone. *Arch Neurol* 2005;**62**:249-254.
27. Molenaar DSM, van Doorn PA, Vermeulen M. Pulsed high dose dexamethasone treatment in chronic inflammatory demyelinating polyneuropathy. *J Neurol Neurosurg Psychiatry* 1997;**62**:388-390.

## **Legend to the Figures.**

Figure 1: Diagram of the Study

Figure 2: Time to clinical deterioration after therapy discontinuation.

Wilcoxon p-values were obtained censoring time respectively at 1, 2 and 3 years. (*The survival curves were obtained using SAS package for PC (version 9.2).*)

**Authorship:**

Eduardo Nobile-Orazio and Francesca Gallia contributed to the conception and design of the study and the preparation of the final protocol. All authors contributed to data acquisition with the exception of Paolo Messina and Ettore Beghi who did the statistical analysis. Eduardo Nobile-Orazio, Paolo Messina and Ettore Beghi analysed and evaluated the results of the study and contributed to the development of the manuscript. All authors critically reviewed and approved the final manuscript.

**IMC (Immunoglobulin Methylprednisolone for CIDP) Trial Group:**

Eduardo Nobile-Orazio, Francesca Gallia (2nd Neurology, Department of Medical Biotechnology and Translational Medicine, Milan University, IRCCS Humanitas Clinical and Research Center, Rozzano, Milan), Dario Cocito, Ilaria Paolasso (Department of Neuroscience, A.O. Città della Salute e della Scienza di Torino, Turin), Stefano Jann, Luisa De Toni Franceschini (Department of Neuroscience, Niguarda Ca' Granda Hospital, Milan), Antonino Uncini, Francesca Notturmo (Department of Neuroscience and Imaging, "G. d'Annunzio" University, SS Annunziata Hospital, Chieti), Giovanni Antonini, Alessandro Clemenzi (Department of Neurology, Mental Health and Sensory Organs, University of Rome "Sapienza", Sant'Andrea Hospital, Rome), Raffaella Fazio, Francesca Bianchi (Department of Neurology, San Raffaele Scientific Institute, INSPE Milan), Angelo Schenone, Elisabetta Fiorina (Department of Neuroscience, Ophthalmology and Genetics, Genoa University, San Martino Hospital, Genoa), Ada Francia, Simona Pontecorvo (Department of Neurology, Umberto I° Policlinico, Rome), Davide Pareyson, Giuseppe Piscoquito (Central and Peripheral Degenerative Neuropathy Unit, IRCCS Foundation, Carlo Besta Neurological Institute, Milan), Lucio Santoro, Fiore Manganelli (Department of Neurosciences, Reproductive Sciences and Odontostomatology, Federico II° University, Napoli), Stefano Tamburin, Maria Luigia Praitano (Department of Neurological and Movement Sciences, Policlinico GB Rossi, Verona University, Verona), Guido Cavaletti, Marialuisa Piatti (Department of Surgery and Translational Medicine, University of Milano-Bicocca, San Gerardo Hospital, Monza) Fabio Giannini, Antonio Torzini (Department of Medical and Surgical Sciences, and Neurosciences, Siena University, Policlinico Le Scotte, Siena), Mario Sabatelli, Marco Luigetti (Department of Neurology, Catholic University, Policlinico Gemelli, Rome), Ettore Beghi, Paolo Messina (Laboratory of Neurological Disorders, IRCCS Mario Negri Institute for Pharmacological Research, Milan), Roberta Macchia, (Medical Affairs, Kedrion SpA, Castelvecchio Pascoli, Lucca), Italy.