5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

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Teaching Course 3

## EAN/PNS: Novel approach in the treatment of neuropathy (Level3)

# Novel therapies in immune-mediated neuropathies

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Milan, Italy

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*EAN Congress, Oslo 2019*

*EAN/PNS Teaching Course*

# *Novel therapies in immune mediated neuropathies*

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HUMANITAS
RESEARCH HOSPITAL

PNS PERIPHERAL NERVE SOCIETY


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## *Conflict of Interest: Eduardo Nobile-Orazio*

- *Steering/Advisory Board: Baxter, Italy; CSL Behring, Switzerland; LFB, France; Kedrion, Italy; Novartis, Switzerland; UCB, UK; Astellas, the Netheralnds*
- *Honorarium for Lectures: Baxter, USA & Italy; CSL Behring, Italy; Grifols, Spain; Kedrion, Italy*
- *Travel grants for Scientific Meetings: Baxter, Grifols, Kedrion, and Novartis, Italy*

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# CHRONIC IMMUNE MEDIATED NEUROPATHIES

1. *Chronic inflammatory demyelinating polyneuropathy (CIDP)*
    1. *Pure motor CIDP*
    2. *Sensory CIDP(Chronic immune sensory polyradiculopathy)*
    3. *Multifocal demyelinating neuropathy (Lewis-Sumner synd)*
    4. *Focal CIDP*
    5. *DADS*
2. *Multifocal motor neuropathy (MMN)*
    1. *Multifocal motor neuropathy without conduction block*
3. *Neuropathy associated with IgM monoclonal gammopathy:*
    1. *Anti-MAG*
    2. *Anti-glycolipid (sulfatide, GM1, GD1a, GD1b, ChSC, ...)*
    3. *Unknown reactivity*
4. *Neuropathy associated with IgG/A monoclonal gammopathy*
    1. *CIDP?*
5. *Paraneoplastic neuropathies*
    1. *Subacute sensory neuronopathy: anti-Hu, not anti-Hu*
    2. *POEMS*
    3. *Others*



## Prevalence of polyneuropathy in the general middle-aged and elderly population

Neurology® 2016;87:1892-1898

Figure 2 Prevalence of polyneuropathy per age decade

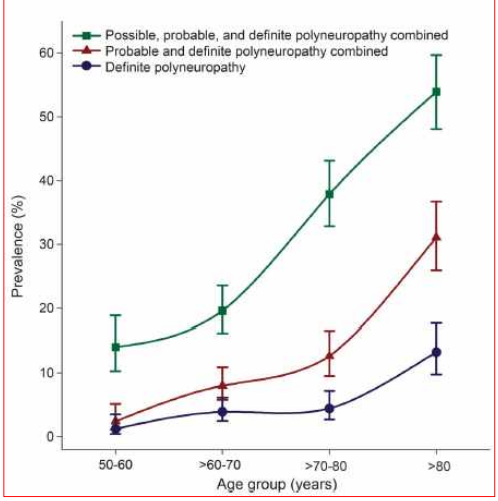


Table 3 Potential causes in cases with definite polyneuropathy

| Associated risk factor present | Cases with a previous diagnosis (n = 37), n (%) | Cases with a new diagnosis (n = 35), n (%) | All cases (n = 72), n (%) |
|---|---|---|---|
| Diabetes | 17 (46) | 5 (14) | 22 (31) |
| Vitamin deficiency[a] | 4 (11) | 6 (17) | 10 (14) |
| Possible alcohol abuse[b] | 2 (5) | 1 (3) | 3 (4) |
| Toxic | 3 (8) | 1 (3) | 4 (6) |
| Hereditary | 1 (3) | — | 1 (1) |
| Immune-mediated[c] | 4 (11) | 3 (9) | 7 (10) |
| Thyroid dysfunction | 2 (5) | 3 (9) | 5 (7) |
| Renal failure | 4 (11) | 1 (3) | 5 (7) |
| Systemic disease[d] | 2 (5) | — | 2 (3) |
| No risk factor present/CIAP | 13 (35) | 20 (57) | 33 (46) |
| Total | 52 (141) | 40 (114) | 92 (128) |

# CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP)

- **Rare diseases** with a prevalence of 1.24 to 8.9/100.000
- **Chronic progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of two or more extremities**, developing over at least 2 months; cranial nerves may be affected
- **Absent or reduced tendon reflexes** in all extremities
- **Elevated cerebrospinal fluid protein** with leukocyte count < $10/mm^3$
- Electrophysiological and/or morphological features of a **demyelinating neuropathy**
- **> 50% of patients severely disabled** at some time

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# 2010 EFNS/PNS Revised Criteria for CIDP

***A Typical CIDP***

- Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developping over at least 2 months; cranial nerves may be affected,

***B Atypical CIDP***

- Motor CIDP
- Sensory CIDP (including chronic immune sensory polyradiculopathy)
- Asymmetric CIDP (MADSAM; Lewis-Sumner syndrome)
- Focal CIDP
- DADS (Distal acquired demyelinating sym.)

*and* Absent/reduced DTR in affected limbs

**Table 1** Major phenotypic variants of CIDP

| CIDP phenotypic variant | Estimated prevalence within CIDP |
|---|---|
| Typical CIDP | 51% |
| Sensory CIDP | 4–35% |
| Chronic immune sensory polyradiculopathy | 5–12% |
| Lewis-Sumner syndrome/ MADSAM | 6–15% |
| Focal CIDP | 1% |
| DADS | 2–17% |
| Acute onset CIDP | 2–16% |
| Motor CIDP | 4–10% |

*Mathey et al,* JNNP *2015*

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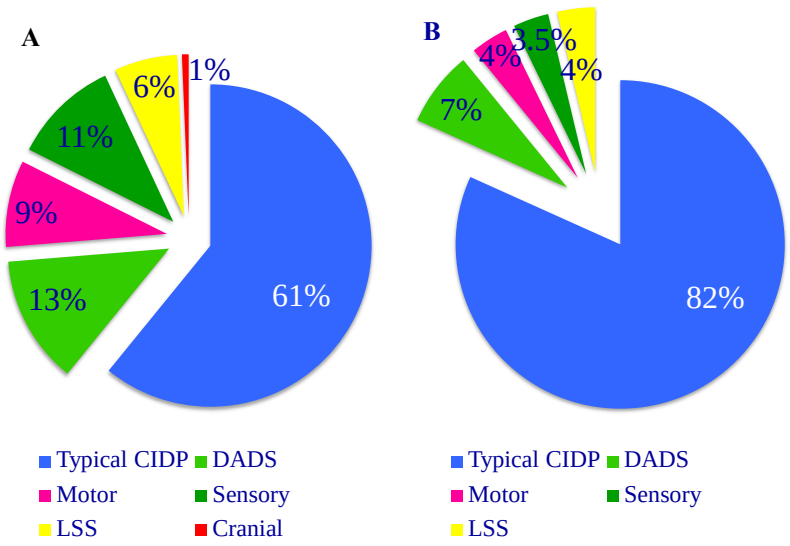
## Atypical CIDP: diagnostic criteria, progression and treatment response. Data from the Italian CIDP Database

Doneddu PE, *et al. J Neurol Neurosurg Psychiatry* 2018;

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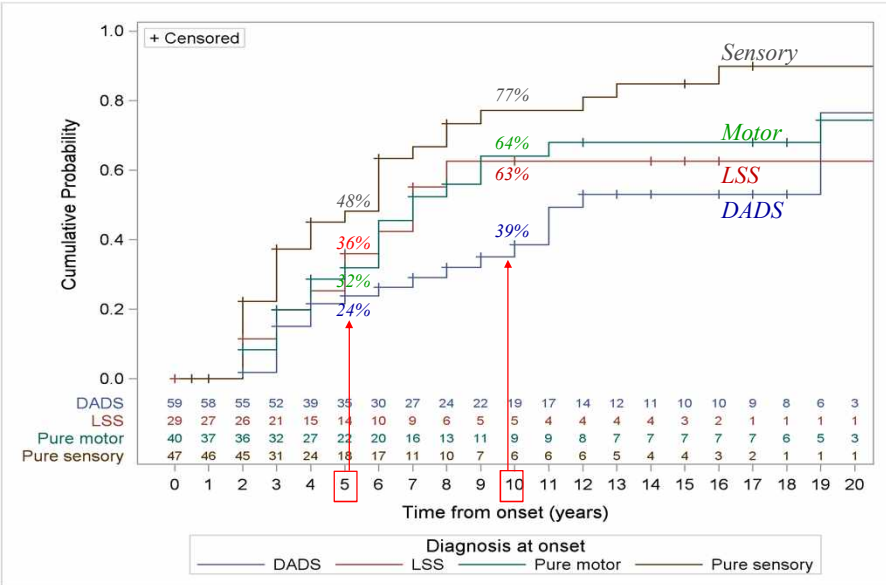
## Time of progression from atypical to typical CIDP

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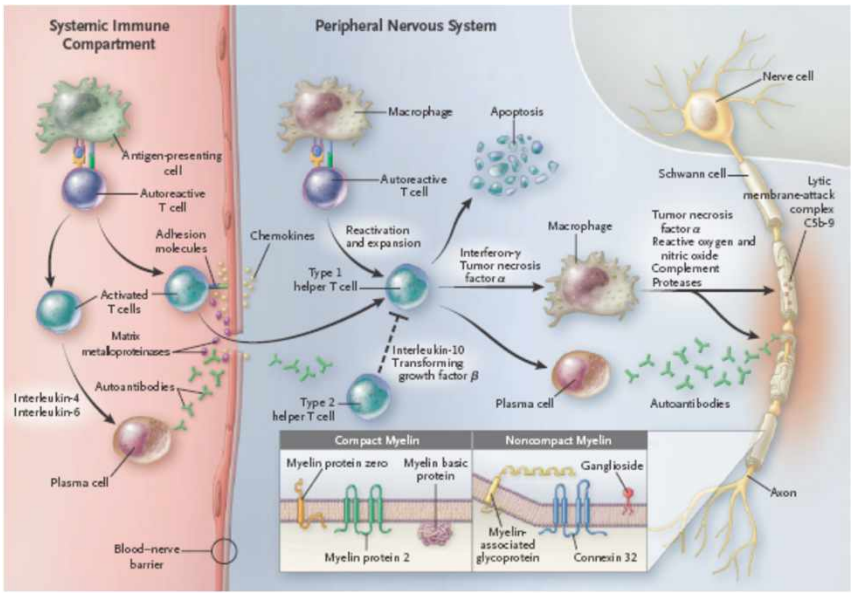
# PATHOGENESIS OF CIDP




*From: Koller, Kieseier, Jander& Hartung (NEJM 2005)*

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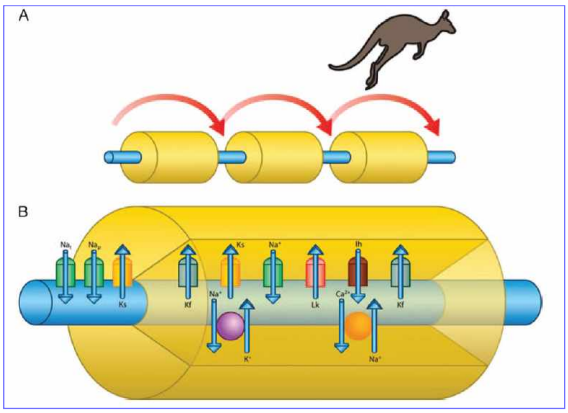
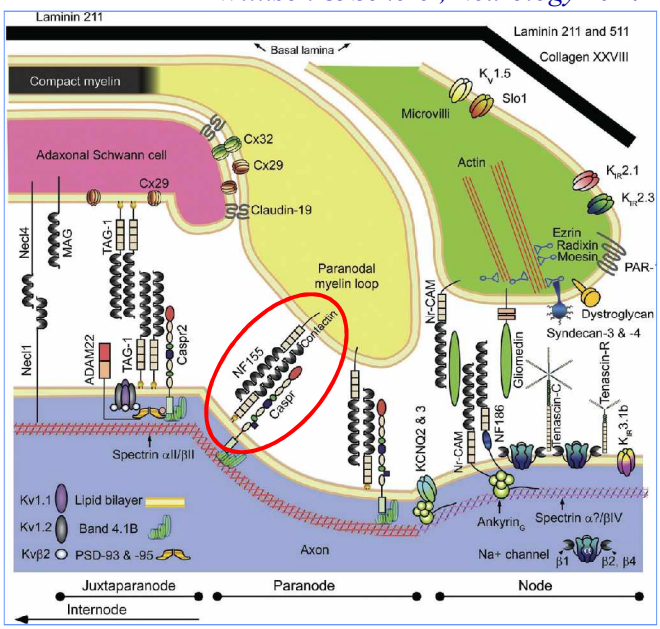



*Krishnan et al, JPNS 2008*

*Willison & Scherer, Neurology 2014*

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# Antibodies to nodal and paranodal proteins in CIDP

| Nodal antigens | | | | |
|---|---|---|---|---|
| Neurofascin 155 | 4/61 | | IgG4 | ELISA |
| | 5/117 | *90/1403 (6.2%)* | IgG4, IgG3; IgM, IgA | ELISA |
| | CIDP 0/16* CCPD 5/7 | | IgG | Cell-based assay |
| | CIDP 4/16* CCPD 6/7 | | Caspr 1 *3/281 (1%)* | ELISA |
| Neurofascin 186 | 1/50* 0/117* | *6/1046 (0.6%)* | IgG | Cell-based assay ELISA |
| Contactin-1 | 3/46† | *26/807 (3.2%)* | IgG | Cell-based assay |
| | 1/50* | | IgG | Cell-based assay |

*Frequency not significantly higher than in healthy controls or other neuropathy controls.
†Contactin-1/caspr-1 in one patient.
CCPD, combined central and peripheral demyelination; IF, immunofluorescence.

*Mathey et al., JNNP 2015; Vural et al., 2018*

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# Therapy for CIDP

THE COCHRANE COLLABORATION®

**CORTICOSTEROIDS FOR CIDP**
*Hughes RAC, Mehndiratta MM & Rajabally YA*
*Cochrane Database of Systematic Reviews 2017*

**PLASMAEXCHANGE FOR CIDP**
*Mehndiratta MM, Hughes RAC, Agarwal P*
*Cochrane Database of Systematic Reviews 2015*

**IVIg FOR CIDP**
*Eftimov F, Winer JB, Vermeulen M,, de Haan R, van Schaik IN*
*Cochrane Database of Systematic Reviews 2013*

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# INITIAL TREATMENT OF CIDP
## *2010 EFNS/PNS Recommendations*

1. Patients with very mild symptoms not/slightly interfering with daily activities may be monitored without treatment.
2. IVIg or corticosteroids should be considered in sensory and motor CIDP in presence of disabling symptoms (Level B). PE is similarly effective (level A) but may be less tolerated. **Contraindications to these treatment should influence the choice** (Good Practice Point)
3. The advantages and disadvantages should be explained to the patient who should be involved in the decision making (Good Practice Point).
4. In pure motor CIDP IVIg should be considered as the initial treatment (Good Practice Point)

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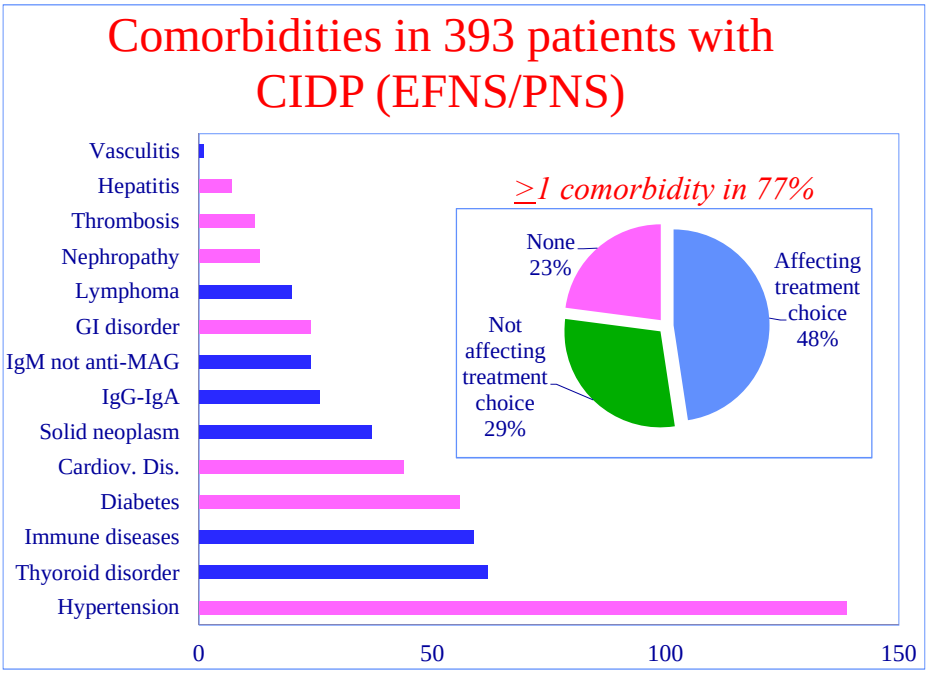
# Comorbidities in 393 patients with CIDP (EFNS/PNS)

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## *OPEN ISSUES IN CIDP TREATMENT*

What therapy should we use in CIDP (IVIg, steroids or PE)?

- Which is the most effective therapy?
- Which has the longer effect?
- Which is the best tolerated therapy?
- Are there predictive factors for therapy response?
- Which is the most convenient therapy?

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**Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomised controlled trial**

*Eduardo Nobile-Orazio, Dario Cocito, Stefano Jann, Antonino Uncini, Ettore Beghi, Paolo Messina, Giovanni Antonini, Raffaella Fazio, Francesca Gallia, Angelo Schenone, Ada Francia, Davide Pareyson, Lucio Santoro, Stefano Tamburin, Roberta Macchia, Guido Cavaletti, Fabio Giannini, Mario Sabatelli, for the IMC Trial Group**

| | **IVMP (n=21)** | **IVIg (n=24)** | p-value |
|---|---|---|---|
| | *n (%)* | *n (%)* | |
| **Success** | **10 (47,6)** | **21 (87.5)** | **0.0085** |

| | **IVMP (n=10)** | **IVIg (n=21)** | p-value |
|---|---|---|---|
| | *n (%)* | *n (%)* | |
| **Relapse** | **0 (0)** | **8 (38.1)** | **0.0317** |

*Lancet Neurol 2012*

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

*Nobile-Orazio et al, JNNP 2014*

| | **IVIg (n=32)** | **IVMP (n=24)** | **p-value** |
|---|---|---|---|
| | *n (%)* | *n (%)* | |
| Improved | **28 (87.5)** | **13 (54.2)** | **0.0072** |
| Median follow-up, months (*range*) | 42 *(1-57)* | 43 *(7-60)* | 0.765 |
| Worsening at follow-up* | 24/28 *(85.7)* | 10/13 *(76.9)* | 0.659 |
| Median months to relapse, *(range)* | **4.5** *(1-24 )* | **14** *(1-31 )* | **0.0126** |

** Including two patients who retired 1 & 7 months after the trial and two who died 1 & 3 months after the trial (3 after IVIg,1 after IVMP)*

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## *OPEN ISSUES IN CIDP TREATMENT*

What therapy should we use in CIDP (IVIg, steroids or PE)?

- Which is the most effective therapy?
- Which has the longer effect?
- Which is the best tolerated therapy?
- Are there predictive factors for therapy response?
- Which is the most convenient therapy?

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# Side-effect of therapy in CIDP

| Therapy | Responder | Non Respond. | Side Effect |
|---|---|---|---|
| **Steroids** *136 (51%)* | **87 (64%)** | **49 (36%)** | **18 (13%)*** |
| **IVIg** *115 (43%)* | **90 (78%)** | **25 (22%)** | **5 (4%)*** |
| **PE** *16 (6%)* | **9 (56%)** | **7 (44%)** | **4 (25%)** |
| **TOTAL** *267* | **186 (69%)** | **81 (31%)** | |

** Steroids vs IVIg: p= 0.02* *Cocito et al., 2010*

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**Table 3** Adverse effects of pulsed steroid treatment vs comparator in CIDP according to the randomized controlled trials of IMC and PREDICT

| | IMC trial IVMP 2 g/month for 6 months | Ref 25 IVIg 2 g/kg/month for 6 months | PREDICT Dexamethasone 40 mg/month for 6 months | Ref 20 Prednisolone 60 mg/day tapered to zero during 6–8 months |
|---|---|---|---|---|
| No. of patients | 21 | 24 | 24 | 16 |
| Weight gain | 8% | 0 | 4%† | 38%† |
| Cushing's face | NA | NA | 25% | 63%* |
| Hyperglycemia | 8% | 4% | 4% | 19% |
| Hypertension | 14% | 8% | 14% | 13% |
| GI symptoms | 13% | 21% | 34% | 38% |
| Insomnia | 8% | 0 | 38%‡ | 76%* |

*Press et al., Acta Neurol Scand 2016*

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## *OPEN ISSUES IN CIDP TREATMENT*

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3. The advantages and disadvantages should be explained to the patient who should be involved in the decision making (Good Practice Point).
4. In pure motor CIDP IVIg should be considered as the initial treatment (Good Practice Point)

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## Different electrophysiological profiles and treatment response in 'typical' and 'atypical' chronic inflammatory demyelinating polyneuropathy

Satoshi Kuwabara, Sagiri Isose, Masahiro Mori, Satsuki Mitsuma, Setsu Sawai, Minako Beppu, Yukari Sekiguchi, Sonoko Misawa

| | Typical CIDP (n=51) | MADSAM (n=30) | p Value |
|---|---|---|---|
| Follow-up period (month) | 65 (15–366) | 82 (16–350) | NS |
| Treatment response | | | |
| Corticosteroid | 83% (38/46) | 72% (21/29) | NS |
| Immunoglobulin | 87% (26/30) | 38% (6/16) | <0.001 |
| Plasmapheresis | 81% (13/16) | 17% (1/6) | 0.0049 |
| No response to any of the above | 0% (0/51) | 23% (7/30) | <0.001 |

*J Neurol Neurosurg Psychiatry* 2014;**0**:1–6.

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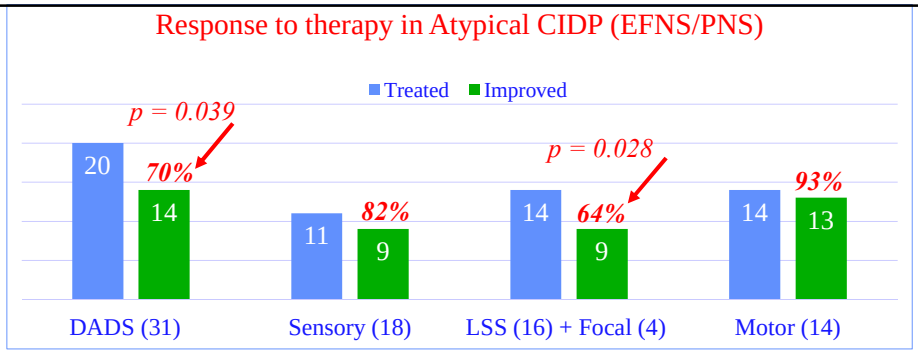


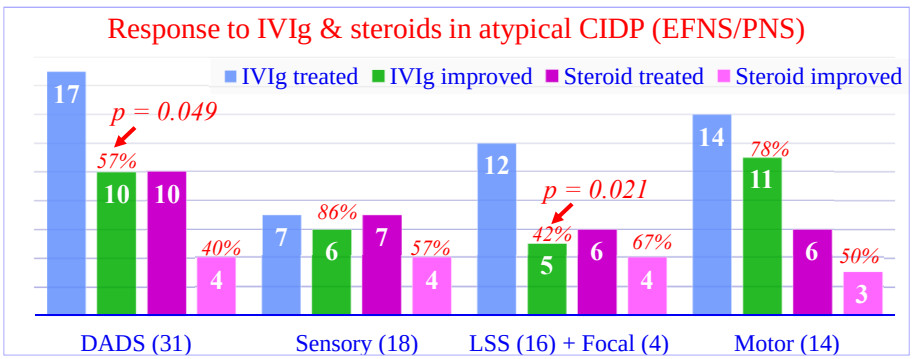


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**TABLE 7** | Treatment response in seropositive chronic inflammatory demyelinating polyneuropathy patients.

| Study | Steroid response | IVIG response | PE response | RTX response | Others |
|---|---|---|---|---|---|
| **Anti-NF155** | | | | | |
| Querol et al. (2014) | 1/4 (partial) | 0/4 | 2/2 | None ($n = 1$) | CY none ($n = 1$) |
| Querol et al. (2015) | – *51%* | – *23%* | – *75%* | Good ($n = 1$) Partial ($n = 1$) | – |
| Ogata et al. (2015) | 5/8 | 4/13 | 4/6 | – | – |
| Kadoya et al. (2016) | Favorable | 3/11 | Favorable | – | – |
| Devaux et al. (2016) | 15/29 | 5/25 | Not good | – | – |
| Garg et al. (2017) | 2/3 | 1/3 | – | Good ($n = 1$) | MMF good ($n = 1$) |
| Burnor et al. (2018) | 1/3 | 1/4 | 3/4 | Good ($n = 3$) | CY good in 1/2 patients |
| **Anti-CNTN1** | | | | | |
| Querol et al. (2013) | 3/3 | 2/3, only partial | – | – | CY no ($n = 1$), AZA partial ($n = 1$) |
| Querol et al. (2015) | – *76%* | – *56%* | – *1/1* | Good ($n = 1$) | – |
| Miura et al. (2015) | 8/11 | 4/10 | – | | CY no ($n = 2$) |
| Doppler et al. (2015a) | - | 3/3 only at initial phase | 1/1, only partial | Good ($n = 1$) | CY good ($n = 1$) |
| **Anti-Caspr** | | | | | |
| Doppler et al. (2016) | 1/1, partial | 0/1 | 1/1 | Good ($n = 1$) | – |
| **Anti-NF186/140** | | | | | |
| Delmont et al. (2017) | 3/5 *60%* | 3/4 *75%* | 1/2 *50%* | Good ($n = 1$) | CY good ($n = 1$) |
| Burnor et al. (2018) | – | 1/1 (temporary) | 1/1 (temporary) | Good ($n = 1$) | CY favorable ($n = 1$) |

*10/12*

*Vural et al. 2018*

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# *OPEN ISSUES IN CIDP TREATMENT*

## What therapy should we use in CIDP (IVIg, steroids or PE)?

- Which is the most effective therapy?
- Which has the longer effect?
- Which is the best tolerated therapy?
- Are there predictive factors for therapy response?
- Which is the most convenient therapy?

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## *YEARLY COST OF THERAPY IN CIDP*

- Steroids:
  - oral prednisone 25-75 mg/d: 220-660 €
  - i.v. methylprednisolone 2g/mos: 850 €
    *(+160 € omeprazole + 60 € Vit D-Ca)*
- Plasmaexchange 12-18/year: 5300-7900 €
  *(effective cost calculated to be 22,000-32,000 €)*
- IVIg: 1-2g/kg/month *(40 €/g):*
  - 60kg: 28,800-57,600 €
  - 80kg: 38,400-76,000 €

*Current price in Italy*

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What to do in CIDP patients not responsive to conventional therapy?

1. *Review the therapy regimen:*
   1. *Steroids dosage and duration of therapy*
   2. *IVIg dosage and frequency*
2. *Reconsider the diagnosis:*
   1. *POEMS*
   2. *Osteosclerotic myeloma*
   3. *Neural B-cell lymphoma*
   4. *Amyloidosis*
   5. *PN+ IgM anti-MAG*
   6. *CMT1a*

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# Response to second therapy in CIDP patients not responsive to initial treatment

| *1st Treat.* | *2nd Treat.* | *No. Treated* | *Responsive* | *Intolerant* |
|---|---|---|---|---|
| **Steroids -> (N=43 )** | **–> IVIg** | 38 | **21 (56%)** | 0 |
| | **–> PE** | 5 | 1 (20%) | 0 |
| **IVIg -> (N=14 )** | **–> STE** | 14 | **6 (43%)** | 1 (7%) |
| **PE - > (5 pt)** | **–> STE** | 5 | **2 (40%)** | 0 |

*Cocito et al., 2010*

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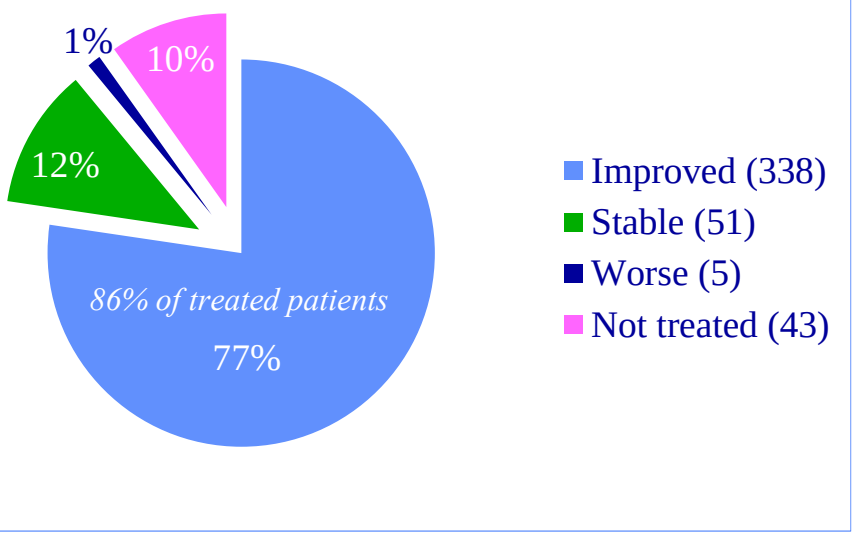
# Response to therapy in 437 patients with CIDP (EFNS/PNS)

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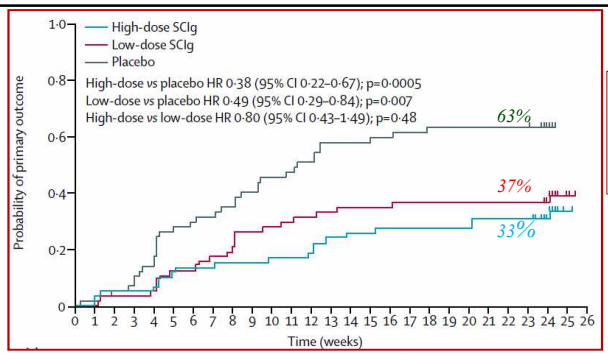
## *IMMUNESUPPRESSANT IN CIDP: WHY ?*

- To treat the 20-30% of patients not responsive to IVIg, steroids or PE
- To treat patients becoming progressively less responsive to IVIg or steroids
- To reduce side effects of chronic steroids
- To reduce the cost of IVIg use
- To reduce patients' dependency from IVIg and Hospital admission






Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial

*Lancet Neurol 2018; 17: 35–46*

Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial

*Lancet Neurol 2008; 7: 136-44*

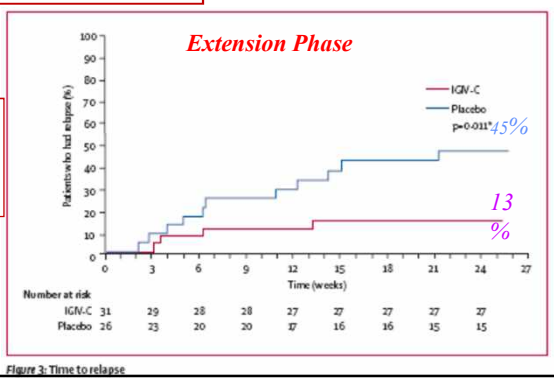



*Figure 3:* Time to relapse

# Advantage of SCIg versus IVIg

- Low Ig levels may lead to **less adverse events** to SCIg than to IVIg (headache, thrombosis and cardiovascular events)
- SCIg **reduce loss of time** and inconvenience for the patients for frequent hospitalization and **reduce hospitalization cost.**
- SCIg **does not require repeated venous access** and may preferrable in some patients
- SCIg may **improve the quality of life** of the patients

*But*

- SCIg may cause **local edema and subcutaneous lassitude** on the injection sites (female?)
- Chronic therapy with SCIg require **frequent subcutaneous injections** in immune neuropathies (2-3 times a week)
- SCIg are **not always as effective as IVIg in immune neuropathy** and a number of patients require periodic IVIg

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# 2010 EFNS/PNS Recommendations for Maintenance Treatment

1. If the first line treatment is effective continuation should considered until maximum benefit, then dose reduced to the lowest effective maintenance dose (Good Practice Point).
2. **If response is inadequate or maintenance doses are high, combination treatments or adding immunosuppressant/ modulatory drug may be considered** (Good Practice Point).
3. Advice about foot care, exercise, diet, driving and life style management should be considered. Neuropathic pain should be treated with drugs according to EFNS guideline (Attal et al 2005, in preparation). Depending on patients' needs, orthoses, physiotherapy, occupational therapy, psychological support and referral to a rehabilitation specialist should be considered (Good Practice Points)
4. Information about patient support groups should be offered to those who would like it (Good Practice Point)

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## Efficacy in open-trial of Immunosuppressant and immunomodulatory drugs in CIDP

| | | |
|---|---|---|
| 1. | Cyclosporin | 82% |
| 2. | Cyclophosphamide | 75% |
| 3. | Rituximab (anti-CD20) | 75% |
| 4. | Methotrexate | 70% |
| 5. | Azathioprine | 64% |
| 6. | Interferon α | 64% |
| 7. | Alentuzumab | 57% |
| 8. | Mycophenolate mofetil | 46% |
| 9. | Interferon β 1a | 35% |
| 10. | Etanercept | 30% |
| 11. | Autologous hematopoietic stem cell transplantation | |

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## Immunomodulatory treatment other than steroids, IVIg & PE for CIDP

Mahdi-Rogers M, Brassington R, Gunn AA, van Doorn PA, Hughes RA
*Cochrane Database of Systematic Reviews 2017 (5)*

- Reviewers' conclusion:

- Four RCT assessing the effect of azathioprine (*27 pts*), interferon β-1a (2 trials, *77 pts*) and methotrexate (*60 pts*) have been performed in CIDP.
- The evidence from these trials does not show significant benefit from any of these therapies but none of the trials was large enough to rule out small or moderate benefit.
- The evidence from observational studies is insufficient to avoid the need for randomized controlled trials to discover whether these drugs are beneficial.

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## Oral fingolimod for chronic inflammatory demyelinating polyradiculoneuropathy (FORCIDP Trial): a double-blind, multicentre, randomised controlled trial

Richard Hughes, Marinos C Dalakas, Ingemar Merkies, Norman Latov, Jean-Marc Léger, Eduardo Nobile-Orazio, Gen Sobue, Angela Genge, David Cornblath, Martin Merschhemke, Carolyn Marie Ervin, Catherine Agoropoulou, Hans-Peter Hartung

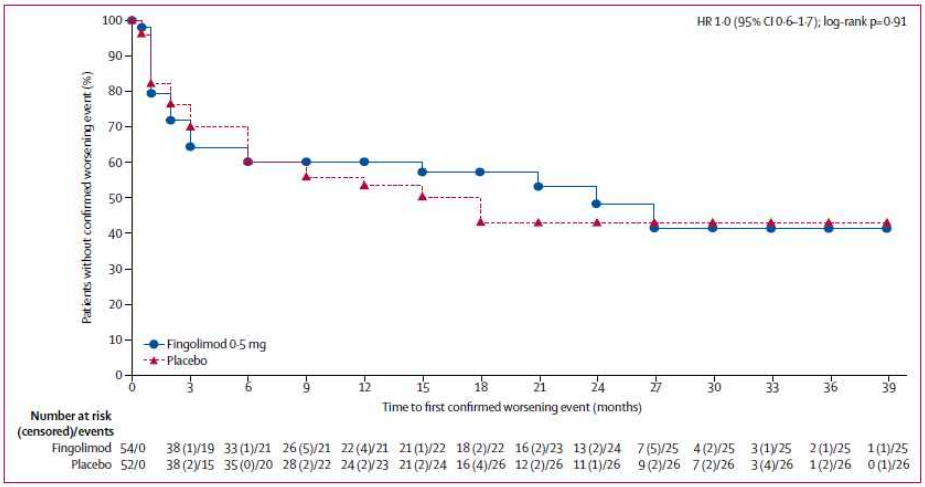


*Figure 2:* Time to first confirmed worsening event

Lancet Neurol 2018; 17: 689–98

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# RITUXIMAB IN CIDP

| Series | Dose | Duration | No of patients | No improved | Notes |
|---|---|---|---|---|---|
| Bodley-Scott 2005 | 700 mg every 3 weeks | 7 courses | 1 | 1 | Self-report |
| Briani 2004; Benedetti 2008; Benedetti 2011 | 375 mg $m^2$ weekly | 4 weeks | 10 | 6 | 3 patients with IgM paraprotein in these series were excluded |
| D'Amico 2012 | 375 mg $m^2$ weekly | not stated | 1 | 1 | |
| Gorson 2007 | 375 mg/$m^2$ weekly | 4 weeks | 2 | 1 | |
| Knecht 2004 | 375 mg/$m^2$ weekly | 7 months | 1 | 1 | With associated Evans syndrome |
| Münch 2007 | 375 mg/$m^2$ weekly | 4 weeks | 1 | 1 | With type 2 diabetes |
| Sadnicka 2011 | 1 g every 2 weeks | 2 doses | 1 | 1 | With Morvan's syndrome and myasthenia gravis |
| Total | | | 17 | 12 | 71% |

*Mahdi-Rogers 2017*

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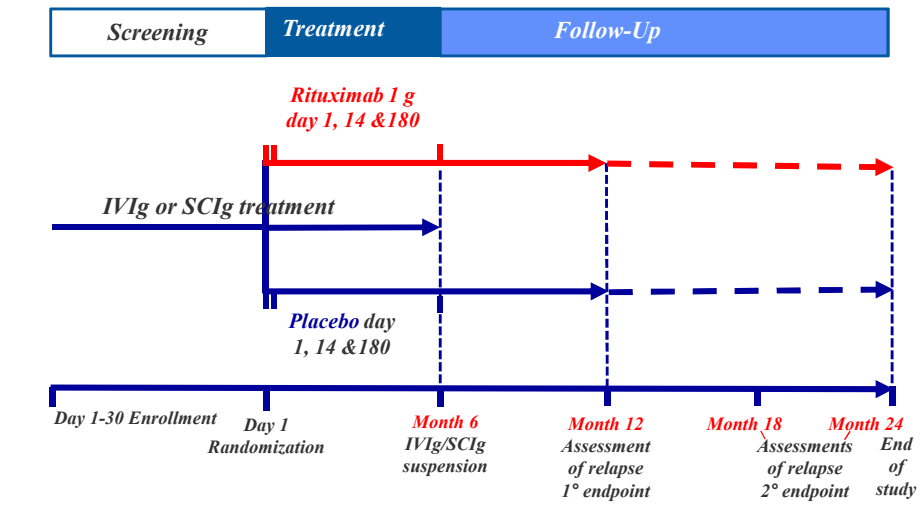
## An Italian Database-based randomized controlled trial with Rituximab in patients with CIDP(CIDPRIT)

### Study Design




*IVIg, intravenous immunoglobulin; SCIg subcutaneous immunoglobulin*

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## *What's going on in CIDP therapy?*

*Ongoing Trials*

- Rituximab (Italy): RCT *CIDPRIT in progress*
- Rituximab (Italy): *opel label in unresponsive CIDP*
- Rituximab (Netherl.): *opel label in unresponsive CIDP*
- Rituximab (Japan): *RCT in anti-NF155 &-CNT1 CIDP*
- Ocrelizumab (USA): *in preparation*
- Alemtuzumab *(USA): pending (suspended ?)*
- SCIg (Intern.): *Hiquvia RCT in progress (Baxter)*
- IVIG (Intern.)*: ProCID RCT dose finding 0.5, 1.0, 2.0 g/kg every 3 wks*
- IVIG (Netherl.): *DRIP RCT of frequent low dose = less frequent high dose*

*Other currently used therapies*

- Cyclophosphamide*, high dose iv, in severe unresponding CIDP*
- HSCT: *reported effective in some therapy refractory*

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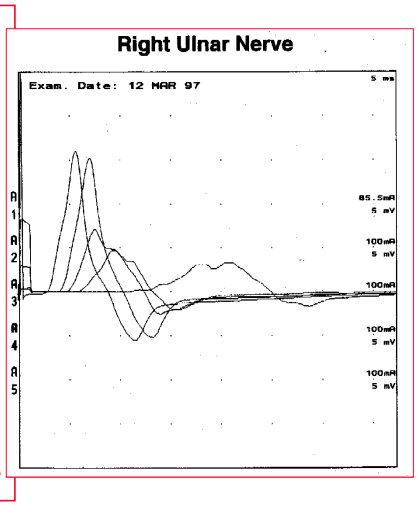
# Multifocal Motor Neuropathy

Rare disorder characterized by:

- progressive, predominantly distal, multineuropathic limb weakness, usually more pronounced in the arms;
- minimal or no sensory loss;
- multifocal persistent partial motor conduction block.
- Frequent (30-50%) association with anti-GM1 IgM antibodies
- Frequent (80%) response to IVIg

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## Distinguishing clinical features of MMN from CIDP, MDN, MND

| | CIDP | MDN | MMN | LMND |
|---|---|---|---|---|
| Weakness Distribution | Symmetric | Multi-neuropathic | Multi-neuropathic | Often asymmetric |
| Arms >legs | no | yes (40-70%) | yes (80%) | sometimes |
| Distal>prox. | no | yes | yes | often |
| Sensory loss | yes | yes | no | no |
| Gen.Areflexia | yes | no | no | no |
| Cranial/bulbar | yes | no | no | yes |

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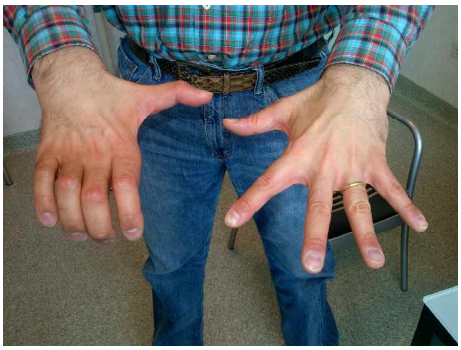
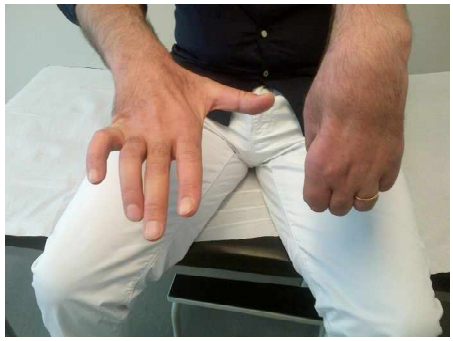
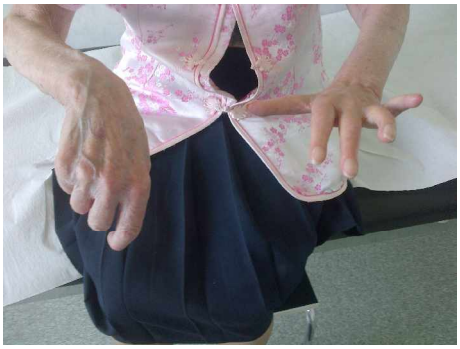

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## EVIDENCES FOR IMMUNE PATHOGENESIS IN MMN

- IgM antibodies to GM1 or other gangliosides are present in 30-50% of MMN patients (*but may be also found in other PN and MND*) and often decrease during clinical improvement;
- Deposits of IgM were found at the nodes of Ranvier of sural nerve in a patient with CB (*and MND*);


- CB can be induced *in vitro & vivo* by serum from MMN patients with and without anti-GM1 IgM;
- Most patients with MMN respond to immune therapies (IVIg).

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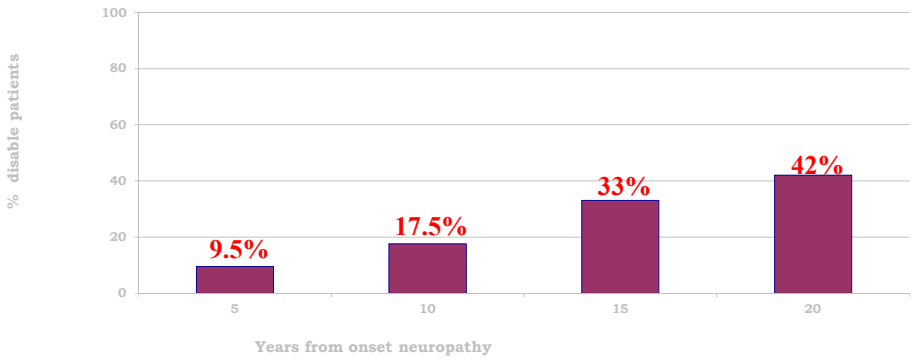
# Disability progression in MMN

| Years of neuropathy | 5 | 10 | 15 | 20 |
|---|---|---|---|---|
| • N° pts | 21 | 17 | 12 | 7 |
| • N° pts Rankin score ≥ 3 | 2 | 3 | 4 | 3 |

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# IMMUNE THERAPIES IN MMN

| Therapy | No. treated | No. (%) improved | No. (%) worsened |
|---|---|---|---|
| Steroids *(alone)* | 64 (62) | 7 (11%) | 14(22%) |
| Plasmaexch.*(alone)* | 21 (20) | 4 (20%) | 2 (10%) |
| IVIg: | 383 | | |
| | ↓↓ impairment: | 303/373 | (81%) |
| | ↓↓ disability: | 91/123 | (74%) |

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# IVIg for Multifocal Motor Neuropathy

*Van Schaik I, van den Berg L, de Haan R, Vermeulen M*
*Cochrane Database of Systematic Review, 2005, April 18*

- Reviewers' summary and conclusion:

- Four RCT assessing the effect of IVIg in MMN have been performed including a total of 34 patients. *(+1 from Baxter)*
- Strength improved in 78% pts treated with IVIg vs 4% with placebo; disability improved in 39% treated and 11% untreated patients
- IVIg has beneficial effect on strength in MMN and provide a non-significant trends toward improvement in disability
- More research is needed to discover whether IVIg improves disability and is cost-effective.

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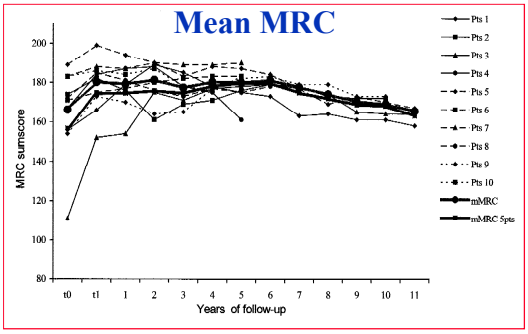
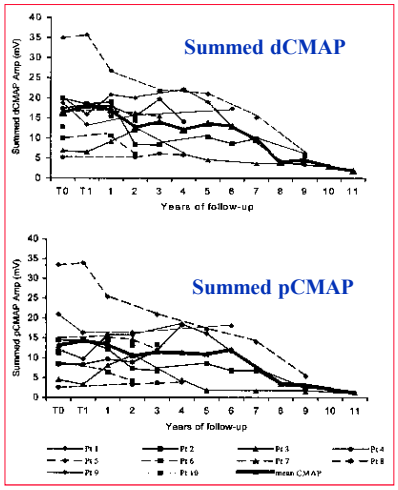
## How long is IVIg effective in multifocal motor neuropathy?

F. Terenghi, MD; A. Cappellari, MD; A. Bersano, MD; M. Carpo, MD, PhD; S. Barbieri, MD, PhD; and E. Nobile-Orazio, MD, PhD

***Neurology 2004***

**10 MMN patients responding to IVIg treated with periodic IVIg infusions for 5-12 yrs (mean 8.2)**

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# SHOULD WE CONSIDER OTHER IMMUNE THERAPIES IN MMN?

- To treat patients not responsive to IVIg
- To treat patients progressively less responsive or unresponsive to IVIg
- To reduce the cost of IVIg use
- To reduce patients' dependency from IVIg and Hospital admission

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Subcutaneous versus intravenous immunoglobulin in multifocal motor neuropathy: a randomized, single-blinded cross-over trial

T. Harbo[a], H. Andersen[a], A. Hess[b], K. Hansen[c], S. H. Sindrup[d] and J. Jakobsen[a]

[a]Department of Neurology, Aarhus University Hospital, Aarhus, Denmark; [b]Department of Clinical Neurophysiology, Aarhus University Hospital, Aarhus, Denmark; [c]Department of Neurology, Rigshospitalet, Copenhagen, Denmark; and [d]Department of Neurology, Odense University Hospital, Odense, Denmark

*Eur J Neurol 2009; 16: 631-8*

*a) 9 patients in a single blinded cross-over study of IVIg vs SCIg*
*b) IVIg (+4.3%) & SCIg (+3.6%) were equally effective for 3 courses*

Subcutaneous immunoglobulin therapy for multifocal motor neuropathy

Filip Eftimov[1], Marinus Vermeulen[1], Rob J. de Haan[2], Leonard H. van den Berg[3], and Ivo N. van Schaik[1]

[1]Departments of Neurology and; [2]Clinical Epidemiology and Biostatistics, Academic Medical Centre, Amsterdam; and [3]Department of Neurology, Rudolf Magnus Institute of Neuroscience University Medical Centre Utrecht, Utrecht, The Netherlands

*J Periph Nerv Syst 2009; 14: 93-100*

*a) 5/5 deteriorated or did not tolerate 50% reduced SCIg*
*b) 4/5 maintained for 6 mos improvement with equal dose of SCIg*

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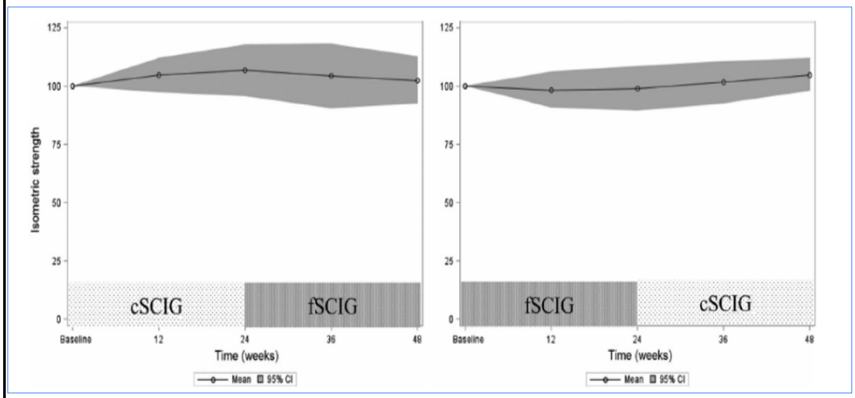
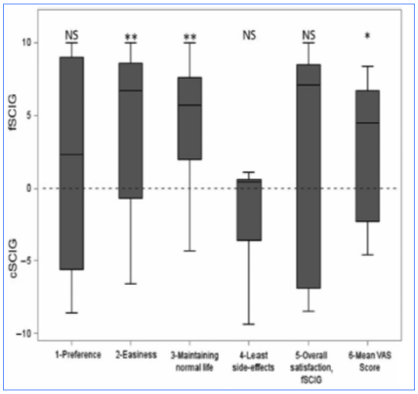
## Randomized trial of facilitated subcutaneous immunoglobulin in multifocal motor neuropathy

A. Al-Zuhairy[a], J. Jakobsen[a], H. Andersen[b], S. H. Sindrup[c] and L. K. Markvardsen[b]




*The relative frequency of localyzed side-effects at the injection site was higher in the facilitated SCIg*

*European Journal of Neurology* 2019, **0**: 1–8

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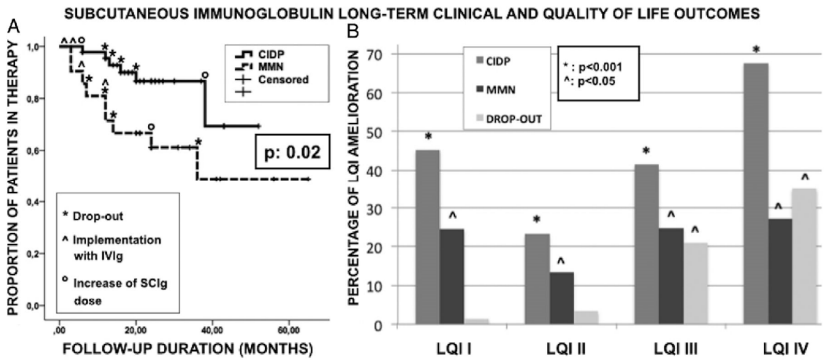
***(A) Survival curves representing the long-term adherence to SCIg therapy in CIDP (solid line) and MMN (dashed line); (B) LQI showed the higher rate of amelioration in CIDP, although a significant improvement versus baseline values was also reported in MMN patients.***




***Dario Cocito et al. J Neurol Neurosurg Psychiatry***
***doi:10.1136/jnnp-2014-310280***

JNNP

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# OTHER IMMUNE THERAPIES IN MMN

| Therapy | No. treated | No. (%) improved |
|---|---|---|
| Cyclophoshamide i.v. | 40 | 30 (75%) |
| " " oral | 6 | 3 (50%) |
| Interferon-β1a | 15 | 8 (53%) |
| Azathioprine, *(alone)* | 10 *(4)* | 5 *(2)* (50%) |
| Rituximab | 28 | 17 (61%) |
| Eculizumab | 13 | 7 (54%) |
| Mycophenolate | 1 | 0 |
| Cyclosporine | 2 | 2 |

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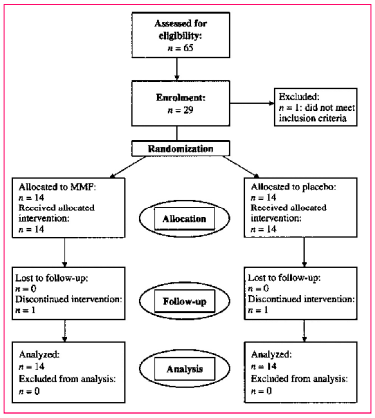
doi:10.1093/brain/awm144 Brain (2007), 130, 2004–2010

## Mycophenolate mofetil as adjunctive therapy for MMN patients: a randomized, controlled trial

Sanne Piepers, Renske Van den Berg-Vos, W-Ludo Van der Pol, Hessel Franssen, John Wokke and Leonard Van den Berg

Department of Neurology, Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, the Netherlands

- *28 pts randomized*
- *1 pt with **MMF** ↓↓ IVIg by 50%.*
- *No signif. ↓↓ of IVIg after 12 mo.*
- *Pts did not have drug toxicity.*
- *No signif. progression after 12 mo*
- *Muscle strength, FS unchanged after 3 months & GMI-IgM after 12 months.*




***Adjunctive MMF was safe but did not alter MMN course or allow IVIg reduction***

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## TREATMENT OF MMN
## 2010 EFNS/PNS RECOMMENDATIONS

1. IVIg (2 g/kg over 2 to 5 days) should be considered as first line treatment (Level A recommendation) when disability is sufficiently severe to warrant treatment.
2. Steroids are not recommended (Good Practice Point).
3. If IVIg is initially effective, repeated IVIg should be considered (Level C) and its frequency guided by the response (Good Practice Point). Typical treatment regimens are 1 g/kg every 2 to 4 weeks, or 2 g/kg every 1 to 2 months (Good Practice Point).
4. *Only* if IVIg is not sufficiently effective immunosuppression may be considered. Cyclophosphamide, interferon β1a, cyclosporin, azathioprine are possible agents (GPP).
5. Toxicity makes cyclophosphamide less desirable (GPP)

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BIOMETRA

ASNP

PNS PERIPHERAL NERVE SOCIETY

Neuromuscular & Neuroimmunology Serv.,
Dept. Medical Biotechnology &
Translational Medicine,
IRCCS Humanitas Clinical Institute
Milan University,
Rozzano, Milan, Italy

Pietro Doneddu
Giuseppe Liberatore
Francesca Gallia
Fabrizia Terenghi
Claudia Giannotta
Antonella Scarale

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# LONG-TERM IVIg THERAPY IN MMN

- *Azulay et al., J Neurol Neurosurg Psychiatry 1997*
  - 8/12 (66%) responding pts required repeated Ig x 9-48 mos, uneffective in 3 after 3 mos; 2 (11%) in remission after 1 yr.
- *Van den Berg et al., Brain 1998*
  - 6/7 (86%) responding pts required weekly Ig (0.4g/kg/wk) x 2-4 yrs (follow-up); 3 (43%) had some deterioration.

***Periodic IVIg are necessary in most MMN patients***

Editorial

Neurology 2000;55:1246–1247

## IVIg treatment improves multifocal motor neuropathy

### Easy to start but difficult to stop

P.A. van Doorn, MD, PhD; and F.G.A. van der Meché, MD, PhD

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PAPER

## Axon loss is an important determinant of weakness in multifocal motor neuropathy

J T H Van Asseldonk, L H Van den Berg, S Kalmijn, R M Van den Berg-Vos, C H Polman, J H J Wokke, H Franssen

J Neurol Neurosurg Psychiatry 2006;77:743–747. doi: 10.1136/jnnp.2005.064816

Table 4 Logistic regression analysis for the determinants of weakness

| Determinant | Univariate | p Value | Multivariate | p Value |
|---|---|---|---|---|
| Axon loss | 5.7 (2.9 to 11.1) | <0.001 | 4.4 (2.0 to 9.7) | <0.001 |
| Conduction block | 7.1 (2.6 to 19.4) | <0.001 | 2.1 (0.7 to 6.6) | NS |
| Demyelinative slowing | 6.6 (3.1 to 14.0) | <0.001 | 2.0 (0.8 to 4.8) | NS |
| Years untreated | 1.1 (1.1 to 1.2) | <0.001 | 1.1 (1.0 to 1.2) | <0.01 |
| Years treated | 1.0 (0.9 to 1.2) | NS | 1.1 (0.9 to 1.3) | NS |
| Nerve length | 2.1 (1.4 to 3.1) | <0.001 | 1.9 (1.1 to 3.2) | <0.05 |

Table 3 Relation between disease duration and the percentage of nerves with weakness, axon loss, conduction block, and demyelinative slowing

| Disease duration (years) | No of patients | Percentage of nerves with* | | | |
|---|---|---|---|---|---|
| | | Weakness | Axon loss | Conduction block | Demyelinative slowing |
| 0–5 | 4 | 24 | 54 | 5 | 3 |
| 5–10 | 7 | 44 | 55 | 12 | 27 |
| 10–15 | 6 | 60 | 65 | 27 | 42 |
| 15–20 | 3 | 86 | 73 | 27 | 55 |

*For each disease duration category, the total number of nerves with abnormalities was assessed and expressed as a percentage of the total number of nerves within that category.

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# IMMUNE THERAPY FOR CIDP

- IVIg, PE & steroids are effective in CIDP;
- PE is less suitable for the long term treatment;
- IVIg are more frequently effective and often better tolerated than steroids but steroids, when effective, have a more prolonged effect;
- Subcutaneous Ig may avoid repeated IVIg infusions
- Despite the number of open studies, no RCT supports the efficacy of immune suppressant in CIDP and should be limited to non responding/intolerant patients or to RCT



Classifications and treatment responses in chronic immune-mediated demyelinating polyneuropathy

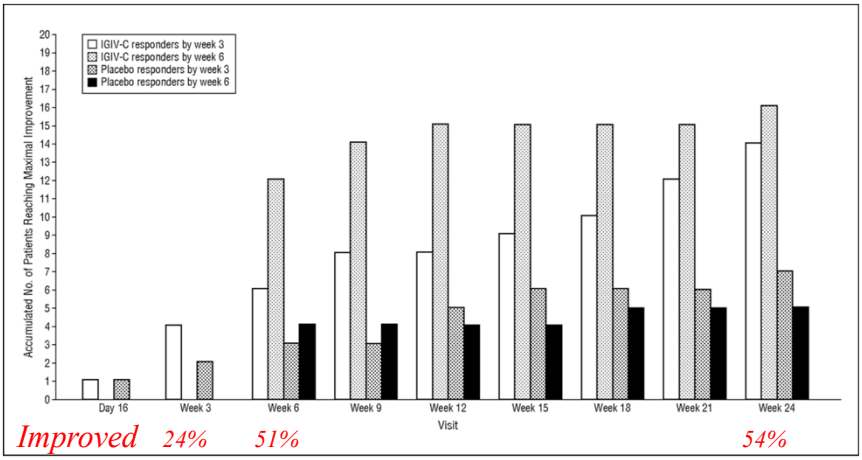
*Tackenberg et al Neurology 2007*

| | CIDP | DADS | MADSAM |
|---|---|---|---|
| n | 36 | 19 | 8 |
| Full clinical remission, n (%) | 4 (11) NS | 8 (42) $p < 0.02$ | 0 (0) NS |
| No immunosuppressive treatment*, n (%) | 4 (11) | 4 (57) | 2 (25) |
| IVIg treated, n | 27 | 13 | 5 |
| IVIg improved, n (%) | 22 (81) | 11 (85) | 4 (80) |
| Mean improvement after I VIg. modified Rankin score ± SD | 1.31 ± 0.69 | 1.07 ± 0.70 | 1.17 ± 0.75<br>p<0.05 |
| Steroid treated, n total; n first line | 20; 5 | 6; 1 | 3; 1 |
| Steroid improved n total; n first line (%) | 13; 4 (65) | 4; 0 (67) | 3; 1 (100) |

# Timing and Course of Clinical Response to Intravenous Immunoglobulin in Chronic Inflammatory Demyelinating Polyradiculoneuropathy

*Norman Latov, MD, PhD; Chunqin Deng, PhD; Marinos C. Dalakas, MD; Vera Bril, MD; Peter Donofrio, MD; Kim Hanna, MSc; Hans-Peter Hartung, MD; Richard A. C. Hughes, MD; Ingemar S. J. Merkies, MD; Peter A. van Doorn, MD; for the IGIV-C CIDP Efficacy (ICE) Study Group*

*Arch Neurol. 2010;67(7):802-807.*




*Improved* *24%* *51%* *54%*

**Figure 1.** Responders who reached maximal improvement. Cumulative number of responders in immune globulin intravenous, 10% caprylate/chromatography purified (IGIV-C) and placebo groups reaching maximal adjusted Inflammatory Neuropathy Cause and Treatment score improvement.

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# 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: 245-53*

*Ivo N van Schaik, Filip Eftimov, Pieter A van Doorn, Esther Brusse, Leonard H van den Berg, W Ludo van der Pol, Catharina G Faber, Joost CH van Oostrom, Oscar J M Vogels, Rob D M Hadden, Bert U Kleine, Anouk G W van Norden, Jan J G M Verschuuren, Marcel G W Dijkgraaf, Marinus Vermeulen*

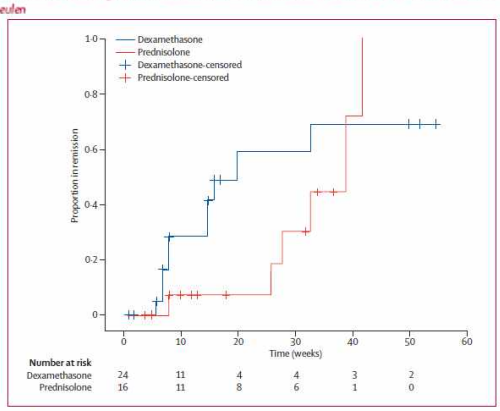


*Figure 3:* Time to reach remission

*Median time to INCAT improvement:*

- *Dexamethasone: 17 weeks*
- *Prednisone: 39 weeks*

- *Oral dex: 13/24 (54%) improved/remitted (40mg/dx4d every 28d x6)*
- *Oral pred: 8/16 (50%) improved/remitted (60mg/d x5 wks, in 27wk)*

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## Response to immune suppressive/modulatory agents in 110 CIDP patients (158 procedures)

| | Treated | Responders | % | % with SE |
|---|---|---|---|---|
| **AZA** | 77 | 21 | **27** | **21** *(13% stop)* |
| **RTX** | 18 | 4 | **22** | **11** |
| **CsA** | 12 | 3 | **25** | **50** *(41% stop)* |
| **CYP** | 13 | 5 | **38** | **15** *(8% stop)* |
| **MTX** | 12 | 2 | **17** | **8** |
| **MFM** | 12 | 3 | **25** | **17** |
| **IFNβ** | 3 | 0 | **0** | |
| **IFNα** | 11 | 4 | **36** | **9** |

*Cocito et al, 2011*

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| Initial diagnosis in MMN | |
|---|---|
| MMN | 31 (35) |
| Motor neuron disease | 28 (32) |
| Mononeuropathy | 11 (13) |
| Polyneuropathy | 13 (15) |
| Radiculopathy | 2 (2) |
| Chronic inflammatory demyelinating neuropathy | 1 (1) |
| Hereditary neuropathy | 1 (1) |
| Minor stroke | 1 (1) |

*Cats et al. Neurology 2010*

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Journal of the Peripheral Nervous System 15:295–301 (2010)

*EFNS/PNS MMN GUIDELINE*

European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of multifocal motor neuropathy. Report of a Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society – first revision

Joint Task Force of the EFNS and the PNS†

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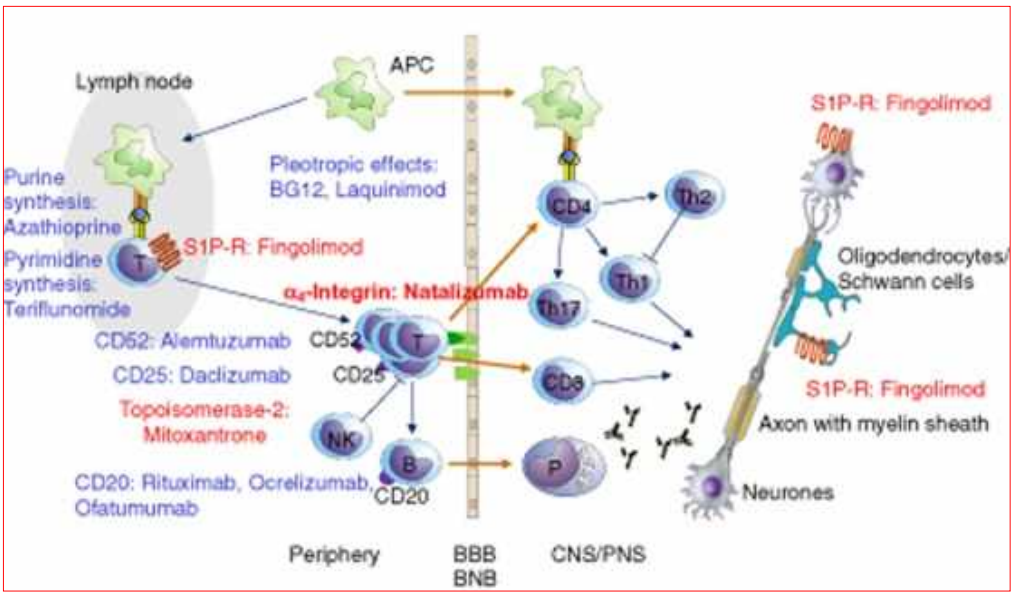


*Melzer & Meuth, Clin Exp Immunol, 2014*

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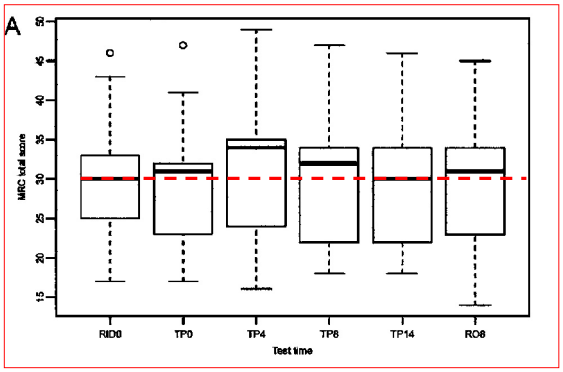
## An open label clinical trial of complement inhibition in multifocal motor neuropathy

Amanda M. Fitzpatrick[1,2], Cameron A. Mann[3], Sarah Barry[4], Katie Brennan[1,2], James R. Overell[2], and Hugh J. Willison[1,2]

*J Peripher Nerv Sys 2011; 16: 84-91*

- 13 MMN patients treated with eculizumab for 14 weeks, in 10 with concomitant IVIg
- Primary outcome: safety of eculizumab; secondary:change in IVIg, performance & NCS.
- Adverse events were minor
- 9/10 patients continued IVIg at the same dosage
- A small effect in some patients (subjective & in some scores)




*MRC Sum score*



## Immunosuppressant & Immunomodulatory treatments for MMN

*Umapathi T, Hughes RAC, Nobile-Orazio E, Leger JM*
*Cochrane Database of Systematic Reviews 2015*

### Reviewers' conclusion:

- In the only RCT, mycophenolate mofetil did not significantly improve strength or function or reduce the need for IVIg
- The use of corticosteroids, and occasionally plasma exchange, has been associated with deterioration.
- There are some reports of benefit but also of serious adverse events from cyclophosphamide either as a primary agent or for patients who do not respond or lose their response to IVIg or require frequent infusions
- There is still little or no evidence about azathioprine, β interferon, rituximab or ciclosporin,
- Trials of IS should be undertaken but non-randomised studies do not suggest a particular favourite candidate.

Journal of the Peripheral Nervous System 15:1–9 (2010)

EFNS/PNS CIDP GUIDELINES

# 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 – First Revision

Joint Task Force of the EFNS and the PNS†

*Peter YK Van den Bergh, Robert DM Hadden, Pierre Bouche, David R Cornblath, Angelika Hahn, Isabel Illa, Carol L Koski, Jean-Marc Leger, Eduardo Nobile-Orazio, John Pollard, Claudia Sommer, Pieter A van Doorn, and Ivo N van Schaik*

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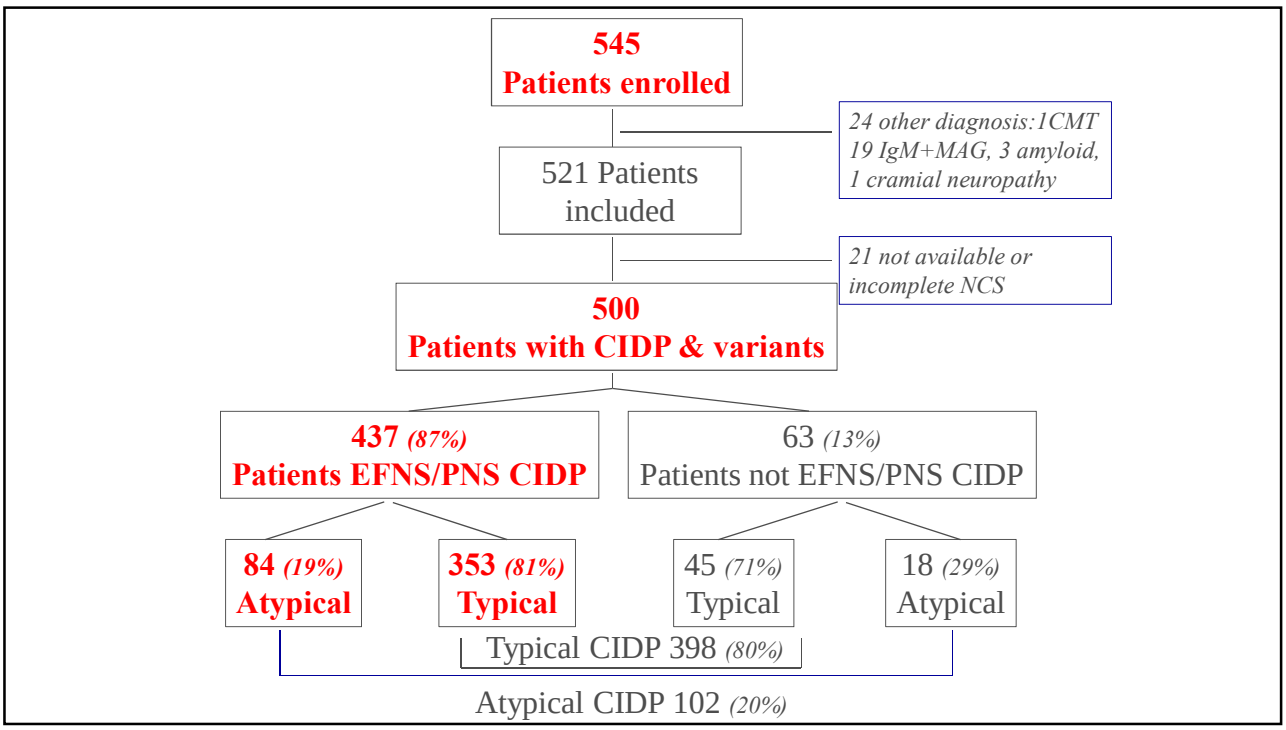


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## Long-term remission of CIDP after pulsed dexamethasone or short-term prednisolone treatment

*Eftimov et al, Neurology 2012*

- 39/40 patients included (median follow-up 4.5 yrs).
- Cure (5 yrs off therapy) or remission in 10/39 patients (26%) after 1-2 courses of dexamethasone or daily prednisolone
- *50% of patients in remission after treatment relapsed after 17.5 months for dexamethasone, and 11 months for prednisolone.*
- *Alternative diagnosis in 7/12 (58%) not responders* (18% of included patients)

*- 10/24 (42%) in remission with oral dex. 40mg/d x 4d every 28days x 6 cycles*
*- 6/16 (37.5%) in remission with oral pred. 60mg/d x 5 weeks, tapered in 27wk*

*Lancet Neurol 2010; 9: 245-53*

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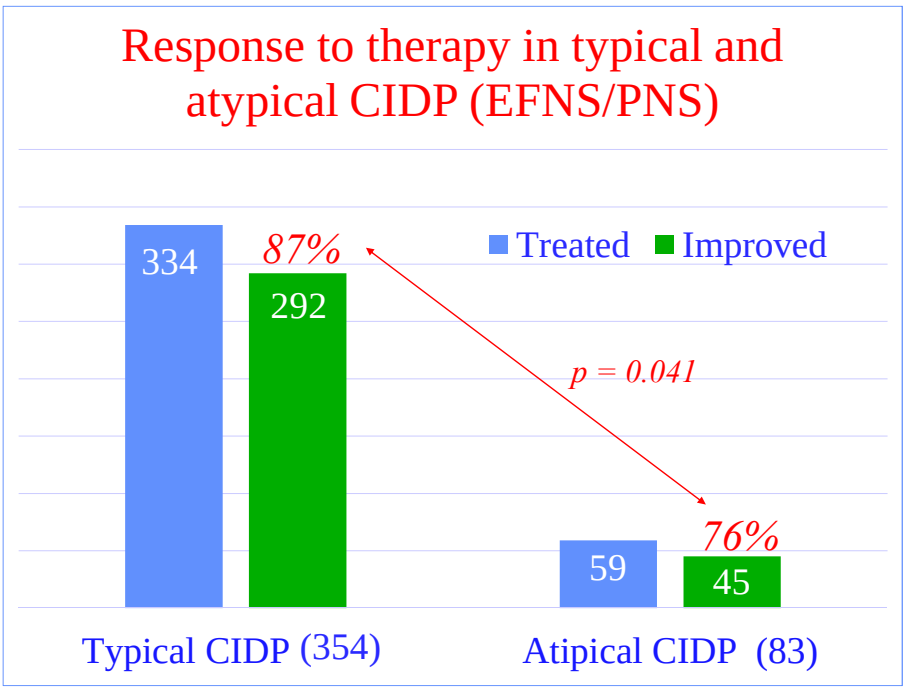
## Response to therapy in typical and atypical CIDP (EFNS/PNS)

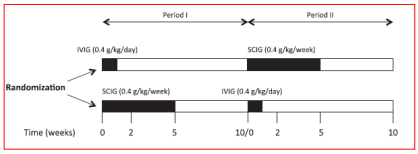



72

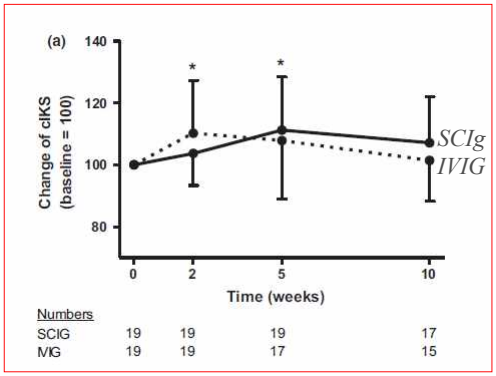
## Subcutaneous immunoglobulin as first-line therapy in treatment-naive patients with chronic inflammatory demyelinating polyneuropathy: randomized controlled trial study

L. H. Markvardsen[a], S. H. Sindrup[b], I. Christiansen[c], N. K. Olsen[d], J. Jakobsen[c] and H. Andersen[a], On behalf of The Danish CIDP and MMN Study Group

*European Journal of Neurology* 2017, **24:** 412–418




*20 CIDP patients*




**Results:** All participants received both therapies, 14 completing the protocol. Overall, cIKS increased by 7.4 ± 14.5% ($P = 0.0003$) during SCIG and by 6.9 ± 16.8% ($P = 0.002$) during IVIG, the effect being similar ($P = 0.80$). Improvement of cIKS peaked 2 weeks after IVIG and 5 weeks after SCIG.

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## Subcutaneous immunoglobulin as first-line therapy in treatment-naive patients with chronic inflammatory demyelinating polyneuropathy: randomized controlled trial study

L. H. Markvardsen[a], S. H. Sindrup[b], I. Christiansen[c], N. K. Olsen[d], J. Jakobsen[c] and H. Andersen[a], On behalf of The Danish CIDP and MMN Study Group

**Table 2** Changes of secondary parameters: Medical Research Council (MRC) score, grip strength, nine-hole peg test (9-HPT), 40-m walk test (40-MWT), overall disability sum score (ODSS) and plasma immunoglobulin G (IgG)

| | | Week | | | |
|---|---|---|---|---|---|
| | Treatment | 0 | 2 | 5 | 10 |
| MRC score (points) | SCIG | 83.9 ± 5.1 | 84.8 ± 5.3 | 85.7* ± 5.2 | 85.0* ± 5.1 |
| | IVIG | 84.0 ± 5.3 | 84.8 ± 5.5 | 85.7† ± 5.6 | 84.5 ± 5.6 |
| Grip strength (kg) | SCIG | 27.0 ± 15.9 | 27.4 ± 16.3 | 28.7 ± 14.6 | 28.2 ± 13.7 |
| | IVIG | 25.6 ± 13.3 | 27.5 ± 15.3 | 27.3 ± 15.6 | 27.7 ± 16.0 |
| 9-HPT (s) | SCIG | 30.2 ± 19.6 | 28.6 ± 17.0 | 29.0 ± 21.2 | 28.2 ± 21.0 |
| | IVIG | 36.4 ± 45.6 | 34.6 ± 38.8 | 32.3 ± 34.8 | 32.1 ± 35.0 |
| 40-MWT (s) | SCIG | 24.0 ± 5.6 | 23.3 ± 5.8 | 22.5* ± 6.2 | 22.8* ± 7.5 |
| | IVIG | 24.6 ± 7.3 | 24.2 ± 7.9 | 23.4† ± 8.2 | 23.4 ± 8.2 |
| ODSS (points) | SCIG | 3.5 ± 1.6 | 3.3 ± 1.6 | 2.8* ± 1.8 | 2.9* ± 1.7 |
| | IVIG | 3.5 ± 1.4 | 3.1 ± 1.7 | 2.9 ± 2.0 | 3.3 ± 1.7 |
| Plasma IgG (g/L) | SCIG | 11.8 ± 2.5 | 16.7*‡ ± 2.9 | 19.5*‡ ± 2.6 | 13.5*‡ ± 2.7 |
| | IVIG | 11.9 ± 2.6 | 24.6† ± 2.8 | 15.7† ± 2.9 | 12.2† ± 2.8 |

Values are mean ± SD. IVIG, intravenous immunoglobulin; SCIG, subcutaneous immunoglobulin.*$P < 0.05$ vs. week 0 for SCIG, †$P < 0.05$ vs. week 0 for IVIG, ‡$P < 0.05$ to corresponding time point during IVIG.

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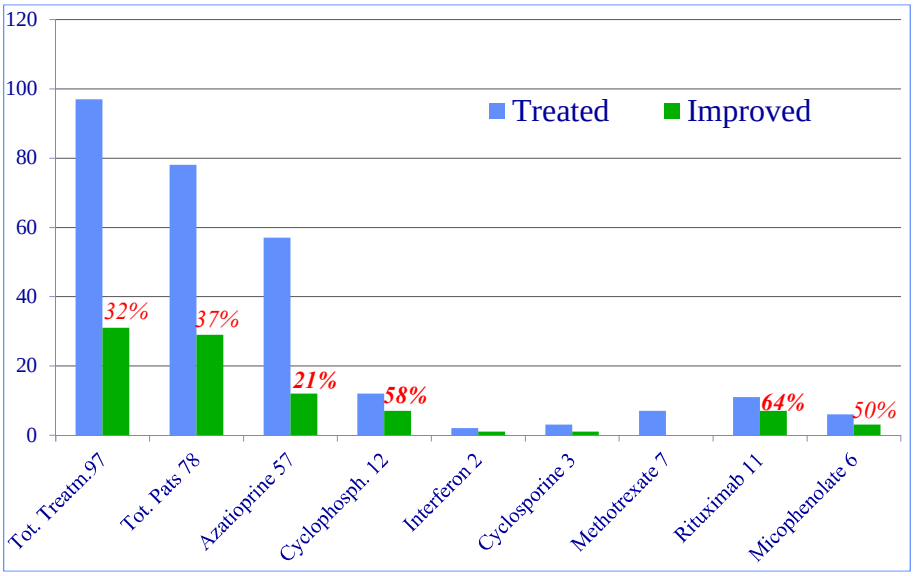
## Immune suppressive therapy in CIDP (EFNS/PNS)






## Reported frequency of atypical CIDP

| References | Number of patients | Reported frequency of atypical CIDP | Mean disease duration |
|---|---|---|---|
| Maisonobe T et al., 1996 | 93 | **56%** | NR |
| Gorson KC et al., 1997 | 67 | 37% | 28 months (2 months-20 years) |
| Rotta FT et al., 2000 | 87 | 49% | 26.3 months (1 week-22 years) |
| Busby and Donaghy, 2003 | 102 | 30% | 72 months (12 months-24 years) |
| Misra UK et al., 2006 | 37 | 22% | 10 months (3 -27.5 months) |
| Rajabally YA et al., 2009 | 46 | 19.6% | 69 months (0–24 years) |
| Viala K et al., 2010 | 146 | 49% | 11 months (0.5 - 200 months) |
| Kuwabara S et al., 2014 | 100 | 40% | 73.5 months |
| Mahdi-Rogers et al., 2014 | 101 | 17.8% | NR |
| Lefter S et al., 2017 | 202 | 1% | NR |

# Our diagnostic criteria for CIDP variants

DADS

1) Symmetric, sensory or predominantly sensory symptoms and signs starting distally in the lower limbs, without proximal limb – trunk - face impairment (*length-dependent fashion*).
   *A) with or B) without increased distal latency*

Pure sensory CIDP

1) Sensory symptoms (including ataxia), without weakness, with a polyneuropathic distribution, symmetric or asymmetric.
2) Symptoms may start anywhere in the body excluding a *length-dependent pattern (included under DADS)*
   *A) with or B) without delayed motor conduction studies*

Pure Motor CIDP

1) Weakness, without sensory symptoms or signs, with a polyneuropathic distribution, symmetric or asymmetric.
2) Symptoms may start anywhere in the body
   *A) with or B) without delayed sensory conduction studies*

Lewis Sumner syndrome

1) Sensory symptoms, with or without weakness, with a multineuropathic distribution *(unilateral focal CIDP included*)
2) Symptoms may start anywhere in the body
   *A) with or B) without motor conduction block*

*Clinical phenotype must have lasted at least one year (temporal criteria)*

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**TABLE 6** | Summary of differences in the clinical phenotype between seropositive and seronegative chronic inflammatory demyelinating polyneuropathy (CIDP) patients.

| | Seropositive CIDP | | | | Seronegative CIDP |
|---|---|---|---|---|---|
| | Neurofascin 155 | Contactin1 | Caspr[a] | Neurofascin 186 | |
| Age of onset, years | 20–30 | 50–60 | 30 | 50–60 | 50–60 |
| Subacute onset | ++ | ++ | ++++ | ++++ | + |
| Tremor | ++ | + | - | - | + |
| Sensory ataxia | +++ | ++++ | - | ++++ | + |
| Severe pain | - | - | ++++ | - | Very rare |
| Central nervous system demyelination | + | - | - | - | Very rare |
| Intravenous immunoglobulin unresponsiveness | ++++ | +++ | ++++ | ++ | ++ |

[a]Based on one CIDP case. Data presented in this table is mainly derived from Ref. (28, 46, 47). Frequencies were determined as follows: ++++ means between 80–100%; +++ means 50–79%; ++ means 20–49%; + means 5–19%; 5% > is very rare.

*Vural et al. 2018*

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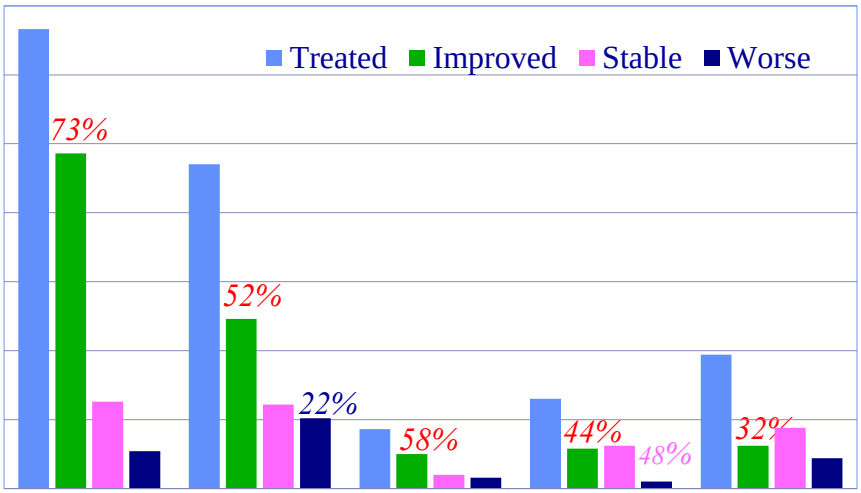
## Response to therapy in 394 treated patients with CIDP (EFNS/PNS)

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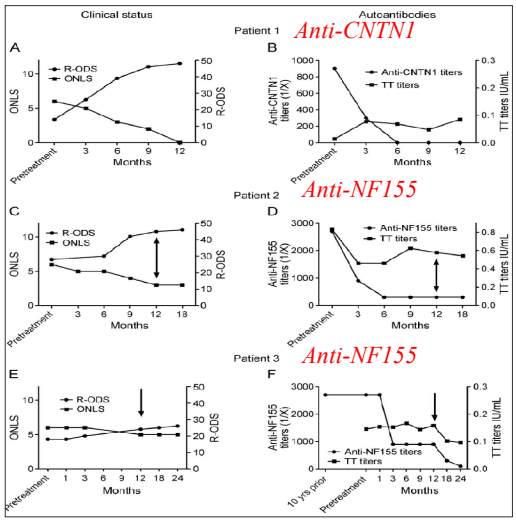
## Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins

- *Four patients with anti-contactin-1/-neurofascin 155 (IgG4) antibodies resistant to IVIg/steroids treated with Rituximab*
- *Two patients markedly improved, one slightly improved and one died for stroke unrelated to therapy*
- *Improvement correlated with the decrease of antibody levels*




*Querol et al., Neurol Neuroimmunol Neuroinflamm 2015*

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*Nobile-Orazio et al. 2013*

**Table 1** Effect of treatment with interferon β, rituximab and eculizumab in multifocal motor neuropathy

| Study | No. of patients | Response to IVIg | Type of study | Dosage | Duration/ follow-up | Response | Improved/ treated |
|---|---|---|---|---|---|---|---|
| Interferon-β1α | | | | | | | |
| Martina et al. [72] | 3 | Unresponsive | pro, ol | 6 MIU, 3 times a week, monotherapy | 6–12 months | 3 improved in walking and manual dexterity, 2 also in disability | 3/3 |
| Van den Berg-Vos et al. [73] | 9 | Responsive | pro, ol | 6 MIU, 3 times a week, monotherapy | 6 months | 6 not improved, 3 improved more than on IVIg | 3/9 |
| Radziwill et al. [74] | 3 | Responsive | pro, ol | 12 MIU, 3 times a week, add-on to IVIg | 9 months | 1 not improved, 2 delayed IVIg by 2 weeks | 2/3 |
| *Total treated/response* | 15 | | | | | | 8/15 (53.3 %) |
| Rituximab | | | | | | | |
| Pestronk et al. [79] | 14 | Insufficient | pro, ol, cont | 375 mg/m$^2$, weekly for 4 weeks + maintenance monotherapy | 2 years | 13 % strength improvement versus 3 % in controls after 1 year, 23 % versus 0 % after 2 years | 18/21, 1 year[a] 13/16, 2 years |
| Rojas-Garcia et al. [80] | 1 | Declining | cs | 375 mg/m$^2$, weekly for 4 weeks, monotherapy | 1 year | No response | 0/1 |
| Ruegg et al. [81] | 1 | Declining | cr | 375 mg/m$^2$, weekly for 4 weeks, yearly for 5 years, add-on to IVIg | 5 years | IVIg frequency reduced from every 7 to every 12 days | 1/1 |
| Gorson et al. [82] | 2 | Responsive | pro, ol | 375 mg/m$^2$, weekly for 4 weeks, add-on to IVIg | 1 year | IVIg reduced by 43 % and strength improved in 1, IVIg increased by 23 % and strength reduced in 1 | ½ |
| Stielgbauer et al. [83] | 3 | Declining | pro, ol | 375 mg/m$^2$ for 2 weeks then 4–6 infusions over 27–39 months, monotherapy | 27–39 months | 3 improved by 5–6 points on muscle strength | 3/3 |
| Chaudhry et al. [84] | 6 | Responsive | pro, ol | 1 g, repeated after 2 weeks, add-on to IVIg | 12 months | No significant change in IVIg dose compared with pre-therapy, 2 patients reduced by 11 % | 0/6 |
| Michaud et al. [85] | 1 | Declining | cr | 375 mg/m$^2$, weekly for 4 weeks, add-on to IVIg | 37 months | No change in IVIg, improved strength and disability | 1/1 |
| *Total treated/response* | 28 | | | | | | 17/28 (60.7 %) |
| Eculizumab | | | | | | | |
| Fitzpatrick et al. [89] | 13 | 10/13 on IVIg | pro, ol | 600 mg at weeks 0, 1, 2, 3 then 900 mg every 2 weeks until week 12 add-on to IVIg in 10 | 14 weeks | 9/10 continued on IVIg at the same dose. No significant improvement but 7/13 subjectively improved | 7/13 (53.8 %) (only subjective) |

*cont* controlled, *cr* case report, *cs* case series, *IVIg* intravenous immunoglobulin, *MIU* million international units, *MMN* multifocal motor neuropathy, *ol* open label, *pro* prospective

[a] Study on 21 patients with antibody-mediated neuropathy including 14 with MMN. Response to therapy not specified for the MMN subgroup

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# *Italian CIDP Database*

*Lombardia Grant on Rare Diseases 2013*


| | | |
|---|---|---|
| 1. | Turin - D. Cocito | 46 |
| 2. | Milan - E. Nobile-Orazio | 50 |
| 3. | Milan - R. Fazio | 40 |
| 4. | Milan - G. Lauria | 10 |
| 5. | Milan - S. Jann | 22 |
| 6. | Milan - G. Cavaletti | 5 |
| 7. | Varese - M. Clerici | 18 |
| 8. | Brescia - M. Filosto | 34 |
| 9. | Treviglio - M. Carpo | 17 |
| 10. | Pavia - A. Cortese | 22 |
| 11. | Padova - C. Briani | 49 |
| 12. | Roma - Marfia | 22 |
| 13. | Bologna- R. Plasmati | 1 |
| 14. | Genova - A. Schenone | 38 |
| 15. | La Spezia - L. Benedetti | 17 |
| 16. | Rome - G. Antonini | 22 |
| 17. | Messina - A. Mazzeo | 24 |
| 18. | Rome - A. Sabatelli | 16 |
| 19. | Naples - L. Santoro | 48 |
| 20. | Pisa - Siciliano | 18 |
| 21. | Palermo - Fierro | 24 |
| 22. | Asolo/Belluno- T. Rosso | 9 |
| | *by April 30, 2019* | *552* |

KEDRION GBS|CIDP Foundation International HUMANITAS RESEARCH HOSPITAL CSL Behring

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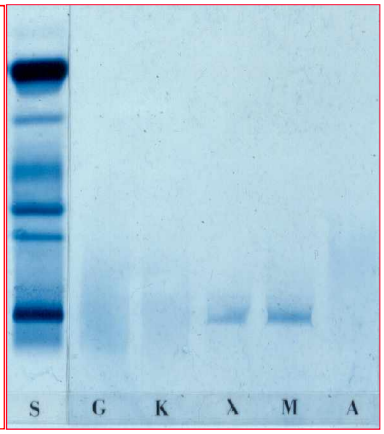
# Neuropathy in Monoclonal Gammopathy

| | |
|---|---|
| Osteosclerotic Myeloma (POEMS) | 50-85% |
| WM | 30-50% |
| MGUS | 5-37% |
| Amyloidosis | 10-20% |
| Cryoglobulinemia | 7-15% |
| Multiple Myeloma | 3-14% |
| Lymphoma | 2-8% |

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# Prevalence of PN in MGUS in relation to isotype

| | No. of patients | **Clinical PN** | Subclinical PN | Total PN |
|---|---|---|---|---|
| Total MGUS | 74 | 8% | 8% | 16% |
| IgG | 34 | 3% | 3% | 6% |
| IgA | 14 | 7% | 7% | 14% |
| IgM | 26 | **15%** | 15% | **31%** |

*IgM vs IgG+IgA: $p < 0.025$* *Nobile-Orazio et al. 1991*

| | PN+MG at our Institute (1984-2000) |
|---|---|
| PN+IgM | 95 (83%) |
| PN+IgG | 15 (13%) |
| PN+IgA | 5 (5%) |

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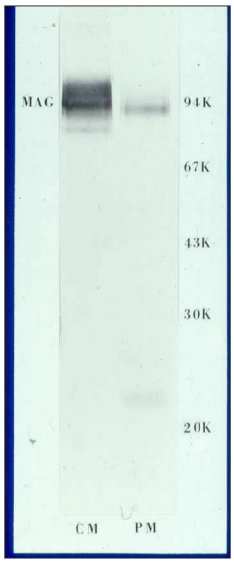
# NEUROPATHY ASSOCIATED WITH ANTI-MAG IgM MONOCLONAL GAMMOPATHY

- Slowly progressive Distal, Acquired, Demyelinating Symmetric (DADS) predominantly sensory, ataxic neuropathy often associated with arm tremor;
- Estimated prevalence of 20/100,000, mostly affecting men aged 50-70 yo;
- Electrophysiologically characterized by signs of a demyelinating neuropathy with disproportionately increased DL compared to CV (increased TLI); conduction block are rare
- Pathologically characterized by demyelination, abnormally spaced myelin lamellae by EM and IgM and complement deposits in nerve by IF






# PN ASSOCIATED WITH ANTI-MAG IgM

Homogeneous clinical and electrophysiological features consistent with a chronic, slowly progressive, predominantly sensory, demyelinating neuropathy

| | MAG + (42) | MAG - (26) | p |
|---|---|---|---|
| *Type of PN* | | | |
| S or S>M | *62%* | 31% | < 0.025 |
| SM | 31% | 38% | n.s. |
| M>S | 7% | *31%* | < 0.01 |
| *NCS Peroneal* | | | |
| Mean MCV | 22.9 m/s | 39.6 m/s | < 0.000001 |
| < 35 m/s | 90% | 23% | < 0.0001 |
| *MGUS/WM-NHL* | *81%*/19% | 27%/*73%* | < 0.0005 |

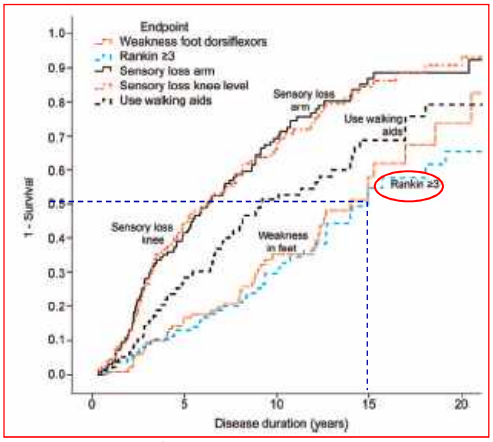
*Nobile-Orazio et al 1994*

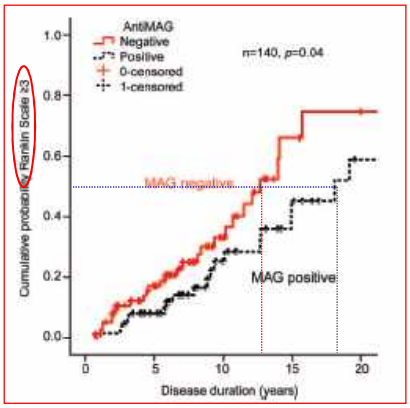
# Prognosis of polyneuropathy due to IgM monoclonal gammopathy

A prospective cohort study

J.M.F. Niermeijer, MD, PhD
K. Fischer, MD, PhD
M. Eurelings, MD, PhD
H. Franssen, MD, PhD
J.H.J. Wokke, MD, PhD
N.C. Notermans, MD, PhD

Neurology® 2010;74:406-412



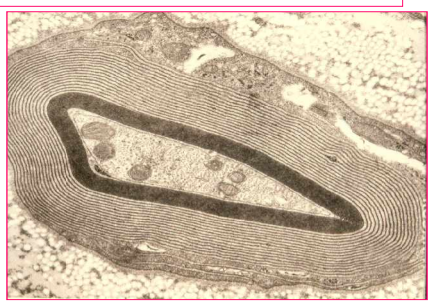



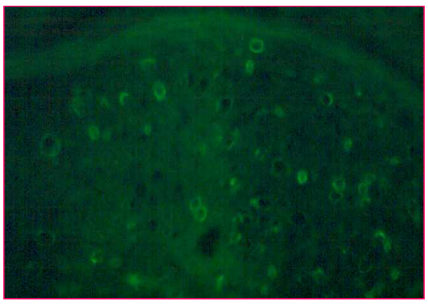

- *140 pts. (72% Dem, 28% Ax, 44% MAG+) followed for 23 yrs:*
- *Demyelination & higher onset age ↑↑ risk of disabiliy, MAG+ ↓↓*



# Pathogenetic role of anti-MAG IgM

1. Anti-MAG IgM are almost invariably associated with PN or predict its onset
2. Clinical & electrophysiological homogeneous features of the neuropathy;
3. Pathological evidence of demyelination and IgM & complement deposits in nerve;
4. Complement mediated nerve demyelination induced in animals by anti MAG IgM;
5. Improvement correlates with reduction of anti-MAG IgM





# RCT in PN & anti-MAG IgM

Plasma exchange (PE)

- Dyck et al 1991: not effective in IgM MGUS
- Oksenhendler 1995: No difference if associated with Chlorambucil

High dose Intravenous Immunoglobulina (IVIg)

- Dalakas et al 1996:: effective in 2/11 IgM (18%) (1/9 MAG, 11%)
- Comi et al 2002: **IVIg slightly better (p=0.05) than placebo**

Interferon Alfa (IFN-α)

- Mariette et al 1997: Sensory improvement in 8/10 IFN-a
- Mariette et al 2000: No difference between IFN-a and placebo.

Oral CTX+ Prednisone

- Niermejier et al 2007: No difference in functional scales with placebo; sensory & DL better at 6 mos.

Rituximab

- Dalakas et al 2009: 4/13 (31%) patients on Rituximab improved by 1 point in INCAT score compared to 0/13 controls (p = 0.096);
- Legér et al 2013: No difference in sensory loss compared to placebo. More pts improved in Hughes scale (20 vs 0%) & self ev. (26.3 vs 4%)

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Cochrane Library

Cochrane Database of Systematic Reviews

## *Rituximab in anti-MAG neuropathy*

***Fig 1: Numbers of patients improved on INCAT score at 8-12 months***

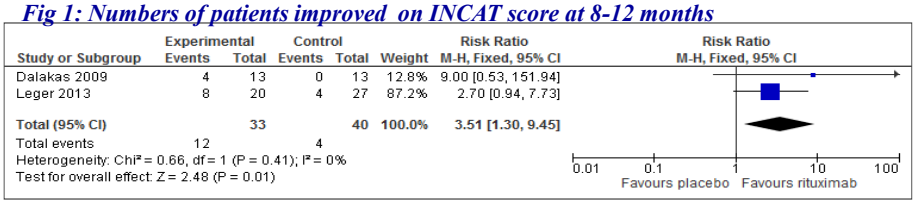



***Fig 2: Improvement in INCAT score (whole and leg disability score) at 8-12 months***

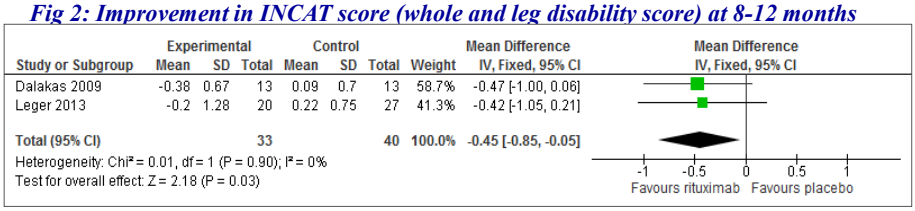
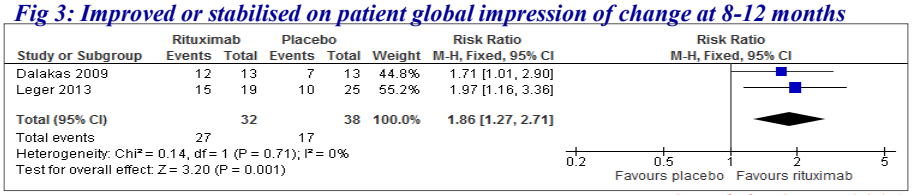



***Fig 3: Improved or stabilised on patient global impression of change at 8-12 months***




*Lunn & Nobile-Orazio2016*

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## *Long-term effect of Rituximab in anti-MAG polyneuropathy*

*Benedetti et al Neurology 2008, 71:1742-37*

- 10 patients with PN & anti-MAG IgM improved at month 12 after Rituximab (375 mg/sq/week x 4 weeks), by ≥ 1 point in 2 of MRC, INCAT or ISS.
- 36 month follow-up
- 8/10 maintained or further improved at month 24
- 6/10 maintained the improvement at month 36
- Anti-MAG IgM reduced by 93% at month 12, 80% at month 24, 60% at month 36.
- All patients deteriorating during follow-up but none of those stable had baseline titers >1/100,000
- CD19+ B cell undetectable at 1 month & in 8 at 1 year

***The benefit of rituximab lasted 24 months in 80% & 36 months in 60% of responding patients***



*Hospital MA et al, Hematologica 2013*

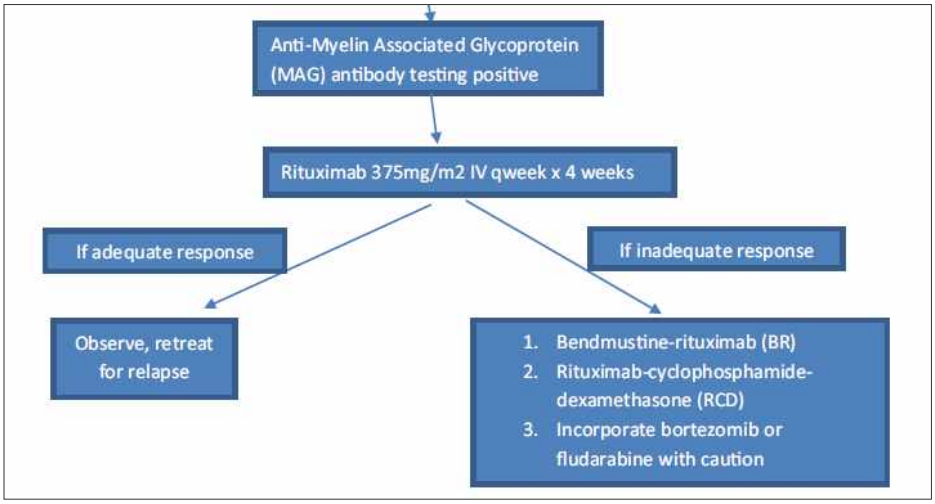
*Immunotherapy-based regimen in anti-MAG neuropathy: results in 45 patients*

Table 2. Patients' characteristics.

| Characteristic | Rituximab combination | Rituximab alone |
|---|---|---|
| N. of patients | 19 | 26 |
| Median age, y (range) | 68 (42-85) | 67 (47-86) |
| Gender: male/female | 12/7 | 14/12 |
| Lymphoplasmacytic cell bone marrow infiltration, n. (%) | 8 (42%) | 10 (38%) |
| Spike IgM level, g/dL (range) | 0.38 (0-1.8) | 0.35 (0-1.52) |
| Anti-MAG titer, BTU (range) | 60000 (1000->70000) | 61000 (5800->70000) |
| Clinical presentation | | |
| Pain | 14 (73%) | 22 (84%) |
| Ataxia | 18 (9%) | 17 (65%) |
| Motor deficit | 11 (58%) | 14 (54%) |
| Sensory deficit | 19 (100%) | 25 (96%) |
| Modified Rankin Score before treatment | 3:7 patients (37%)<br>4:12 patients (63%) | 2: 8 patients (30%)<br>3:13 (50%)<br>4:5 (20%) |
| Modified Rankin Score after treatment | 1:5 patients (26%)<br>2:10 patients (53%)<br>3:3 patients (11%)<br>4:1 patients (5%) | 1:10 patients (39%)<br>2:11 patients (42%)<br>3:5 patients (19%) |
| Previous treatment, n. (%) | 7 (36%) | 20 (77%) |
| Rituximab | 2 (10%) | 0 |
| Chlorambucil | 4 (21%) | 20 (77%) |
| IgIV | 1 (5%) | 0 |

*8+ CTX*
*7 + Fluda*
*4 + CTX & Fluda*

*Median time to improvement* *5 mos* *9.5 mos* *p= 0.03*

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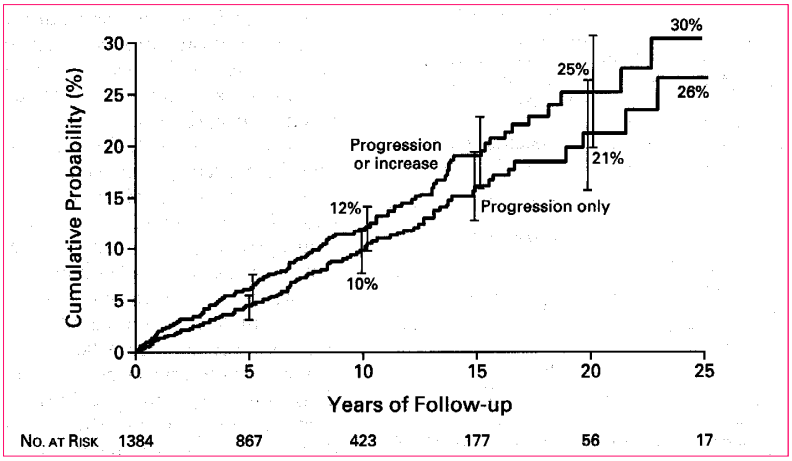
# *Prognosis of MGUS*




- ***10-20% of MGUS become malignant in 10-20 years*** *(~1%/ yr)* *(Kyle et al 2002)*
- ***6% of 50 PN+MGUS developed haematologic malignancy*** *after a mean follow-up of 14 yrs* *(Ponsford et al 2000)*

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