

# Controversies in CIDP treatment



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# Outline



- Accurate diagnosis
  - Variants may respond differently to therapies
  - Identifying underlying disease
- First line therapy
  - Immunoglobulin: IVIg, SCIG
  - Plasma exchange
  - Steroids
- Long term therapy
  - Optimal IVIg dose
  - Second line immunosuppression
- Therapy in refractory cases
  - ?? Rituximab
  - ?? Fingolimod
  - ?? Stem cell therapy
- Outcome measures to assess efficacy

# CIDP



- Commonest treatable chronic neuropathy in the Western world
- Progression over at least 2 months
  - Slowly progressive
  - Relapsing remitting
- Predominant motor symptoms in commonest form
- In the classical form
  - Relatively symmetric involvement of upper and lower limbs in classical form
  - Proximal and distal weakness
- Several variants
  - focal or multifocal
  - Sensory including proximal sensory
- Reduced or absent reflexes
- Elevated CSF protein
- NCS with evidence of primary demyelinating neuropathy
- Multifocal demyelination, remyelination, onion bulbs, inflammatory cells, axonal loss on biopsy (sural nerve biopsy frequently normal)

# CIDP



- Crude prevalence of definite and probable CIDP 2-9/100, 000
  - McLeod 1999, Lunn 1999, Chio 2007
- Estimated crude annual incidence 0.15 per 100,000 adults
  - McLeod 1999
- 54% of patients become severely disabled (mRS 4 or 5) at some time
  - Lunn 1999
- >10% remain severely disabled despite treatment (13% require aid to walk)
  - Lunn 1999, Chio 2007
- >80% fail to make spontaneous recovery
- >50% still requiring treatment at prevalence date (Lunn 1999)

# CIDP- Disease associations



- IgG & IgA monoclonal gammopathy
- Immunodeficiency virus (HIV)
- Hepatitis C
- Sjögren's syndrome
- Inflammatory bowel disease
- Melanoma
- Lymphoma
- Diabetes Mellitus
- Myeloma

# CIDP differential diagnosis



1. Hereditary eg. CMT 1A, CMT-X
2. Malignancy – Ca, Lymphoma, Myeloma (POEMS)
3. Monoclonal gammopathy – IgM Paraproteinaemia
4. Multifocal Motor Neuropathy with Conduction Block
5. Recurrent G.B.S.
6. Metabolic – diabetes, uraemia, hypothyroidism, acromegally
7. Drug induced – Amiodarone, N-hexane, perhexilene
8. HIV Infection and Lyme Disease

# CIDP variants



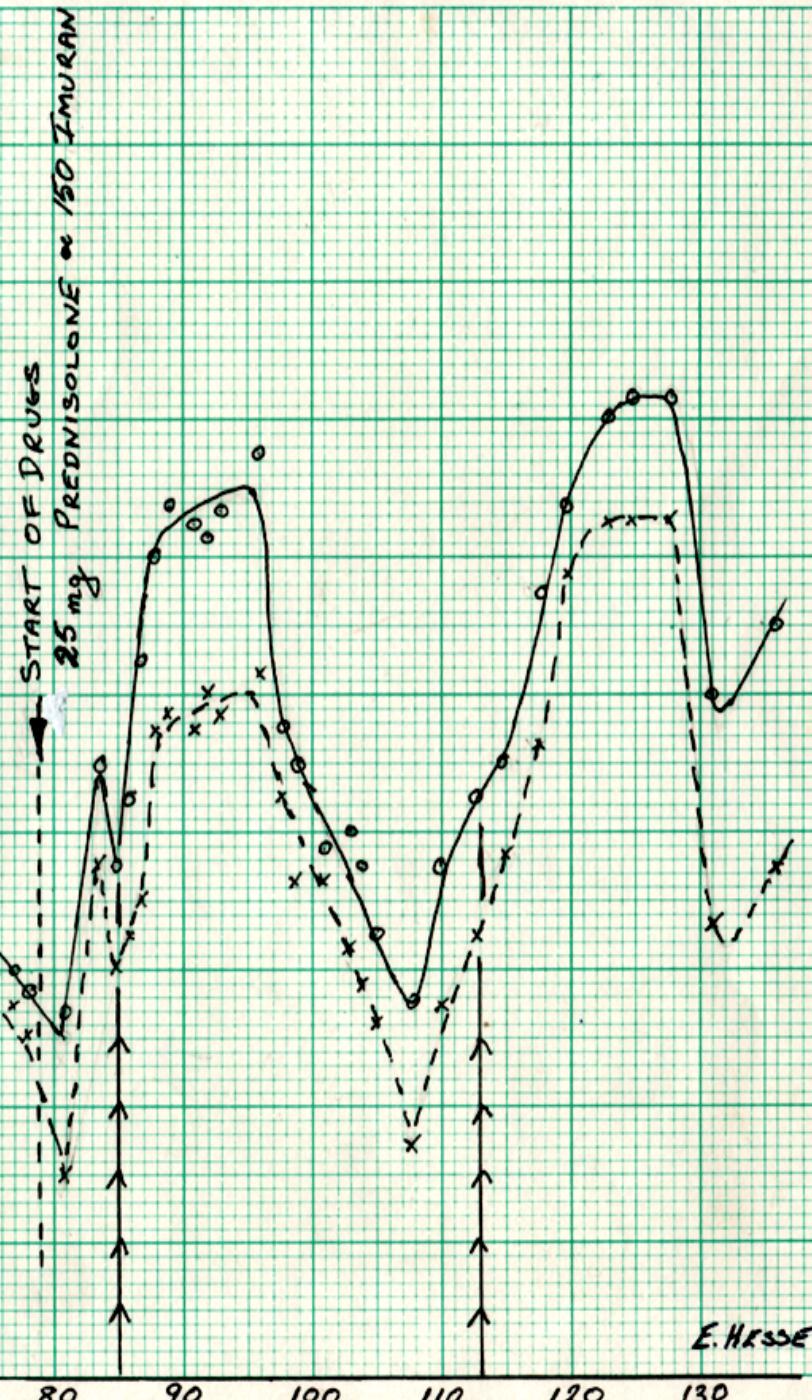
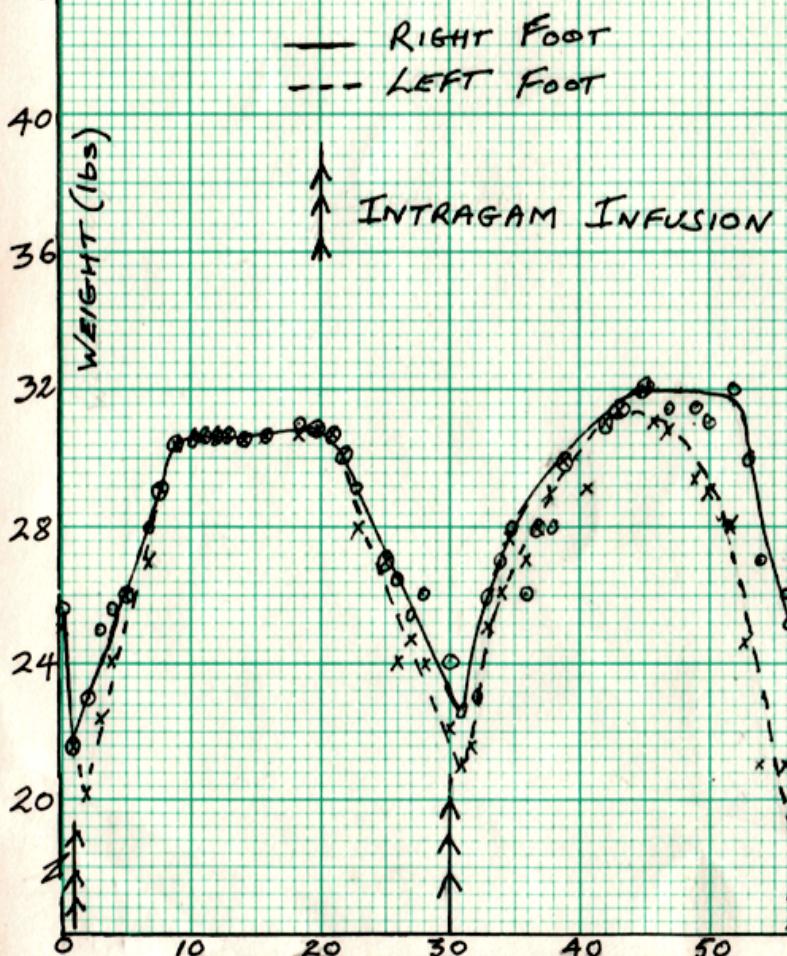
- Symmetric proximal and distal motor predominant CIDP
- Lewis-Sumner Syndrome (Multifocal acquired demyelinating sensory and motor neuropathy - MADSAM)
- Monofocal presentations
- Sensory or sensory predominant variants (including CISP)
- Distal acquired demyelinating sensorimotor neuropathy (DADS)
  - With IgM paraprotein
  - Without IgM paraprotein
- CIDP with antibodies to contactin or neurofascin
  - Contactin Abs: aggressive, distal, axonal with no response to IVIg
  - Neurofascin: distal weakness, disabling tremor, ataxia, demyelinating, poor response to steroids, some response to Pex
  - IgG4 related – generally good response to Rituximab
- Demyelinating neuropathy associated with systemic disease
  - HIV
  - Lymphoma
  - **Diabetes**
  - Hepatitis B,C
  - Thyrotoxicosis
  - IgG or IgA MGUS
  - Osteosclerotic myeloma (POEMS)
  - organ or bone marrow transplantation
  - Inflammatory bowel disease
- CIDP with CNS demyelination

JH

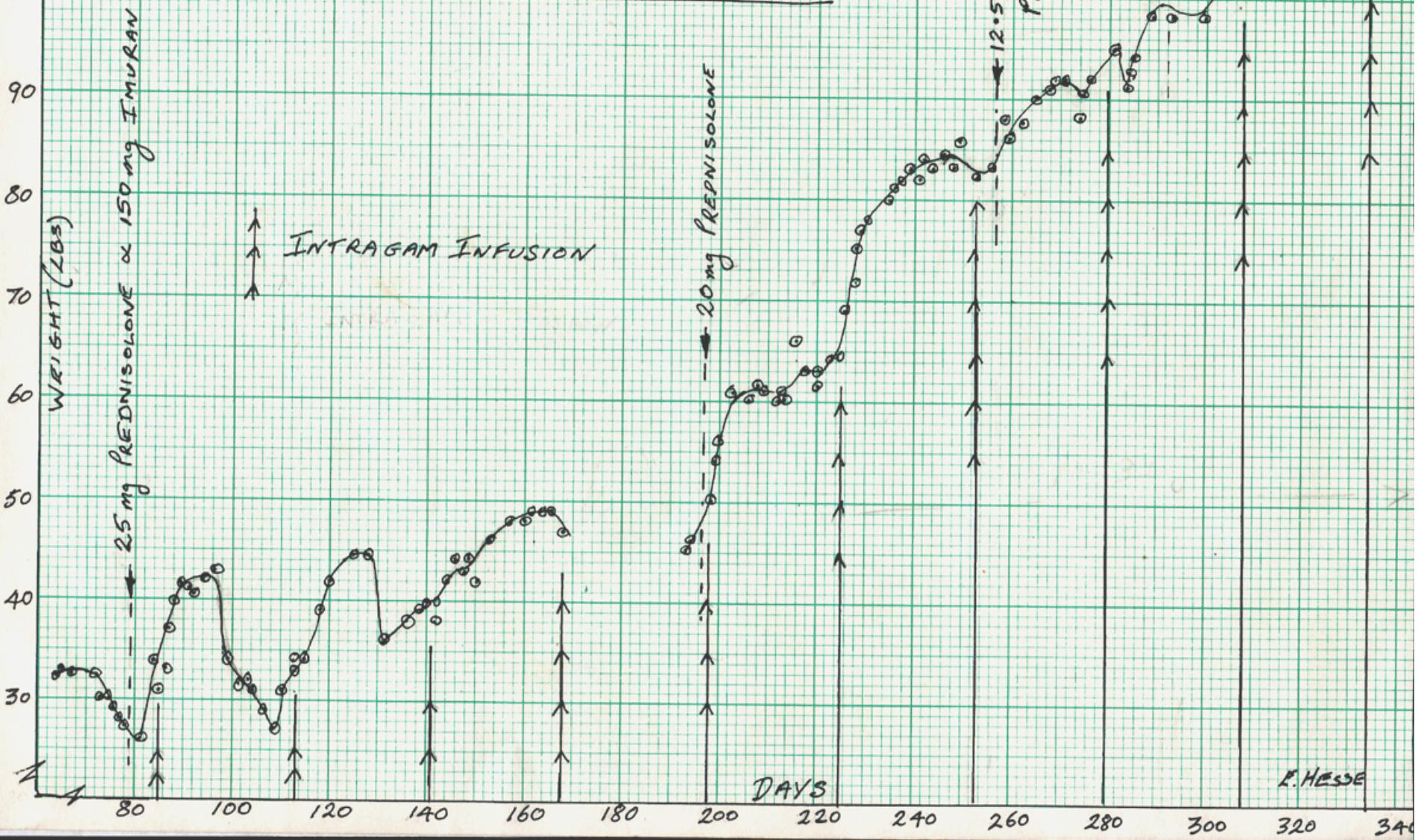


- 55F
- Progressive proximal and distal lower limb weakness over 6-8 weeks
- Unable to walk without assistance
- Minor sensory findings
- NCS consistent with acquired demyelinating neuropathy

GRAPH I: VARIATION OF FOOT STRENGTH  
SHOWING INITIAL TREATMENT



GRAPH 2: VARIATION OF FOOT STRENGTH  
SHOWING PROGRESSIVE TREATMENT



TB



- 19 y.o. female
- 3 month history of difficulty walking and bilateral lower limb weakness, followed by severe upper limb weakness
- minor upper limb sensory symptoms
- on initial examination
  - upper limb power 2/5 (finger flexion /extension 3-3.5/5)
  - lower limb power 4-4.5/5
  - areflexic
  - glove and stocking reduction in pin sensation
  - normal light touch, vibration, joint position
- NCS slowed SNCV, proximal block on motor studies, minimal slowing of MNCV

# TB-progress



- initial plasmapheresis with little benefit
- IVIg- some improvement in leg strength but arms unchanged and subsequent deterioration over next month
- oral prednisone 50mg daily commenced without benefit
- minimal transient improvement after further IVIg
- transient improvement on two occasions after pulse methylprednisolone
- cyclosporin commenced with no improvement over 5 months
- azathioprine, cyclosporin and steroid given in combination and more intensive immunosuppression discussed-  
sustained improvement over the next four months

# IVIg for CIDP



- Cochrane review 2011
- 7 RCTs
  - 5 vs placebo- IVIg superior
  - 1 each vs prednisone and plasmapheresis- no significant difference
- Mainly initial 2g/kg
  - only one trial (*Hughes 2008*) had ongoing maintenance dose 1g/kg/3 weekly
  - trial vs PEx lower IVIg dose (0.4g/kg/week x3 then 0.2g/kg/week x3)
- Crossover or parallel

# IVIg for CIDP

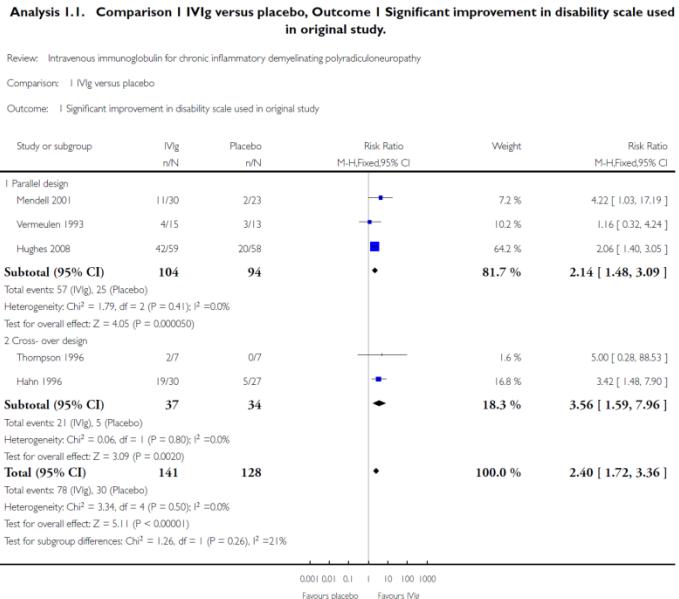


- IVIg vs prednisone
  - Hughes et al *Ann Neurol* 2001
- IVIg vs plasma exchange
  - Dyck et al *Ann Neurol* 1994
- IVIg vs placebo
  - Hahn et al *Brain* 1996
  - Hughes et al *Lancet Neurol* 2008
  - Mendell et al *Neurology* 2001
  - Thompson et al *J Neurol* 1996
  - Vermeulen et al *JNNP* 1993

# IVIg vs placebo



- Significantly  proportion improved within 6w after IVIg than placebo: pooled RR 2.4(1.7-3.4)
- NNT to produce improvement 3 (2.3-3.6)
- significant improvement in 55% of IVIg treatments
- spontaneous improvement in 23-26% of placebo treatments
- Significant mean difference in Rankin score improvement between treated and placebo arms 0.26
- Long term (24w) disability scores only available for the largest trial (Hughes 2008- induction plus maintenance)
  - Mean improvement 1.1 vs 0.3
  - 54% IVIg vs 21% placebo patients had improved at 6m



# SC Ig vs IV Ig in inflammatory neuropathy

- SC Ig equal efficacy with IV Ig
  - Increased patient convenience
  - Probably more steady state IgG levels
  - Potential cost saving  
  - Markvardsen et al Eur J Neurol 2013; 20: 836-4  
Eur J Neurol 2014; 21: 1465-70
  - Lazzaro et al Neurol Sci 2014; 35: 1023-34

# Optimal dose of IVIg



- Monthly dose if IVIg to attain a given Ig level varies widely- should we be measuring levels?
- If dose inadequate what is better- increased dose or frequency?
- *Kuitwaard Ann Neurol 2009*: low  $\text{IgG}$  significantly related to poorer outcome in GBS
- *Vlam et al J Neurol 2013*:  $\text{IgG}$  higher in MMN responders than non responders
- *Kuitwaard et al JNNP 2013 84:859-861*
  - Peak serum  $\text{IgG}$  in 25 stable CIDP patients, fixed IVIg doses and intervals
  - $\text{IgG}$  dose-  $\text{IgG}$
  - $\text{IgG}$  before and shortly after infusion in individual patients v stable over time
  - Subgroup of patients getting q2w IVIg reached a steady state with fairly constant IgG levels

# Optimal dose of IVIg



- ICE study: 2g/kg initially then 1g/kg q2-3w
- SCIG ~~IV~~IgG with each dose less- more steady state
- Various protocols aimed at using minimum effective dose
  - *Lunn et al:*
    - 2g/kg and repeat at 3-6 w if not fully effective
    - Wait until clinical deterioration to determine dosing interval
    - Give 2g/kg twice at determined interval then reduce by 20% of dose until relapse
- Effective assessment tools necessary to optimise dose
- IVIg probably suppressive rather than curative
- When to attempt to withdraw – van Doorn et al ? Most CIDP patients need treatment for 4-5 y
- RMC MTX trial in 44% of patients with placebo add-on IVIg doses could be reduced or withdrawn suggesting frequent over-treatment (*Lancet Neurol* 2009)

Long term remission of CIDP after pulsed dexamethasone or short term prednisolone treatment (PREDICT study)  
Eftimov et al *Neurol* 2012 78:1079-1084



- Multicentre RCT 6 monthly pulses of dxmt vs 8 months of daily oral prednisolone
- 39 patients
- Mean follow up 4.5 years
- “Cure” if >5 years off treatment
- Cure or remission in 26%
- Median time to improvement 4 months for dxmt and 9 m for oral pred
- 50% of those in remission after initial treatment relapsed (median interval 17.5 m for dxmt, 11 m for pred)
- Alternative diagnoses made in 58% of non responders
- ***Cure or long term remission in 25% patients with CIDP after one or two courses of pulsed dexamethasone or daily oral prednisolone***

# 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 IMCT Trial Group\*  
*Lancet Neurol* 2012; 11: 493–502

- CIDP stable for 3m
  - No more than 12.5mg prednisone daily
- Treated for 6m then observed relapse rate in 6m after cessation of treatment
- IVIg 2g/kg or IVMP 2g over 4 days per month for 6 months

# IVIg vs IVMP for CIDP



	IVMP	IVIg
Suspended treatment	52%	12.5%
Responded and continued	48%	88%
Worse/not improved	38%	12.5%
<b>Relapses at 6m in improved</b>	<b>0%</b>	<b>38%</b>
<b>Relapses at 12m in improved</b>	<b>48%</b>	<b>54%</b>
Adverse events	5%	0%
Stopped treatment of own volition	10%	0%

# IVIg vs IVMP for CIDP



- All parameters improved in IVIg group
- Only mRS, Rotterdam scale and QoL measure improved in IVMP
- Only significant difference in NCS was reduced DML in IVIg group
- More sustained freedom from relapse in the IVMP group that responded compared to IVIg responders

# Treatment of chronic inflammatory demyelinating polyneuropathy with high dose intravenous methylprednisolone monthly for five years: 10-Year follow up

Ülkü Türk Börü<sup>a</sup>, Hülya Erdoğan<sup>a</sup>, Recep Alp<sup>b</sup>, Mustafa Tasdemir<sup>c</sup>, Serhan Yıldırım<sup>a,\*</sup>,  
Adnan Bilgiç<sup>a</sup>, Arda Duman<sup>a</sup>, Alper Arslan<sup>a</sup>      Clinical Neurology and Neurosurgery 118 (2014) 89–93

- 20 CIDP patients
- 5 excluded from follow up as treatments not completed
- 15 pts followed for 10 years
- Initial 1g IVMPx10days then 1g q4w for 5 years
- All improved at 6m, 4y, 5y (mRS vs baseline)
- Relapse in 40% of patients at mean 9.5 months after treatment cessation (50% responded to reintroduction of steroids)

# Chronic inflammatory demyelinating polyradiculoneuropathy: search for factors associated with treatment dependence or successful withdrawal

Magalie Rabin,<sup>1</sup> Gurkam Mutlu,<sup>2</sup> Tanya Stojkovic,<sup>1,3</sup> Thierry Maisonobe,<sup>1,4,5</sup>  
Timothée Lenglet,<sup>1,4</sup> Emmanuel Fournier,<sup>1,3,4</sup> Pierre Bouche,<sup>1</sup> Jean-Marc Léger,<sup>3</sup>  
Karine Viala<sup>1,4</sup>     *J Neurol Neurosurg Psychiatry* 2014;85:899–904.

- 40% of treatment responders remain treatment dependent
- 70 treatment dependent CIDP patients
- 36 CIDP patients whose treatment could be discontinued
- Treatment dependent group
  - More multifocal
  - 80% on IVIg
  - More resistant to steroids as first line therapy
  - Longer delay to effective treatment
- Rate of effective withdrawal higher with steroids

# Immunosuppressive agents for CIDP



## Few RCTs

- Azathioprine Dyck et al 1985
  - N=27, AZA 2mg/kg+pred vs Pred alone
  - Not blinded
  - No significant benefit clinical or NCS measures
- Methotrexate RMC Trial group 2009
  - Patients responding to and still on steroids or IVIg
  - 7.5mg weekly 4w, 10mg weekly 4w, then 15mg weekly to 40w
  - Reduction in IVIg or pred from 16w
  - No significant benefit
- Small case series for cyclosporin, mycophenolate, cyclophosphamide, rituximab
- Trial of Fingolimod currently recruiting

# Observational studies



- Azathioprine
  - Dalakas 1981 3mg/kg/day
    - ✖ 3 of 4 steroid resistant patients improved (90-95% N)
  - McCombe 1987 4/7 improved by at least one point on 6 point disability scale

# Cyclophosphamide



Series	Dose	Duration	No. of patients	No. improved	Notes
Prineas 1976	50-150 mg daily	2 to 9 months	4	4	
Dalakas 1981	2 mg/kg	Not stated	1	1	
McCombe 1987	Not stated	Not stated	5	4	
Bouchard 1999	2 mg/kg	6 to 12 months	3	0	Refractory to other treatments
Brannagan 2002	200 mg/kg	4 days	4	4	
Gladstone 2005	Not stated	Median 2.9 years	5	4	Follow up of Brannagan 2002 included the 4 patients in Brannagan and one additional patient
Good 1998	1 g/m <sup>2</sup> monthly	Maximum 6 months	15	12	11 improving to normal
All studies			37	29	

# Cyclosporin

Series	Dose	Duration	No. of patients	No. improved	Notes
Heftner 1990	Not stated	Not stated	1	1	Combination of cyclosporin and plasma exchange
Kolkin 1987	Not stated	Not stated	1	1	
Barnett 1998; Hodgkinson 1990	10 to 8 mg/kg daily after 1 month and 5 mg daily after 3 months but later 3 to 7 mg/kg and then maintained at 2 to 3 mg/kg	Not stated	19	14	11 had side effects
Mahattanakul 1996	not stated	Not stated	8	3	
Matsuda 2004	5 mg daily	Not stated	7	7	Trough dose maintained at 100 to 150 ng/ml
Odaka 2005	3 mg daily	Not stated	5	4	Trough dose maintained at 100 to 150 ng/ml
All studies			41	30	

# Mycophenolate



Series	Dose	Duration	No. of patients	No. improved	Notes
Chaudhry 2001	1000 mg twice daily	Not stated	3	1	
Mowzoon 2001	Not stated	Not stated	2	2	
Radziwill 2006	Not stated	Not stated	6	3	
Benedetti 2004	Not stated	Not stated	2	2	It was possible to reduce the amount of IVIg being used by 50% without any deterioration in their condition
Umapathi 2002	Not stated	Not stated	4	0	
Gorson 2004	Not stated	Not stated	12	3	In the group as a whole there was no significant improvement in average impairment or disability compared with baseline
All studies			29	11	

# Interferon beta



- 2 RCTs of Interferon beta1a (Hadden et al 1999, Hughes et al 2010)
  - No benefit
- Several observational studies

Series	Dose	Duration	No of patients	No. improved	Notes
Choudhary 1995	Six month course of IFNb-1a 22 mcg thrice weekly for 3 weeks and then 44 mcg thrice weekly for 8.5 to 10.3 months	Not stated	1	1	
Kuntzer 1999	Not stated	Not stated	4	2	There was no statistically significant benefit, two patients showed moderate improvement and one relapsed on treatment with IFNb-1a alone
Martina 1999	Not stated	Not stated	1	1	Pure motor (3 other patients with multi-focal motor neuropathy also improved)
Radziwill 2001	22 mcg three times weekly or on alternate days	Not stated	5	4	
Vallat 2003	30 mcg weekly	Not stated	20	7	Ten (50%) remained stable and three (15%) worsened
All studies			31	15	

# Rituximab in CIDP



J Clin Invest. 2012 April 2; 122(4): 1393–1402.  
**Rituximab induces sustained reduction  
of pathogenic B cells in patients with  
peripheral nervous system autoimmunity**

Michael A. Maurer,<sup>1</sup> Goran Rakocevic,<sup>2</sup> Carol S. Leung,<sup>3</sup> Isaak Quast,<sup>1</sup>  
Martin Lukačišin,<sup>1</sup> Norbert Goebels,<sup>4</sup> Christian Münz,<sup>3</sup> Hedda Wardemann,<sup>5</sup>  
Marinos Dalakas,<sup>2,6</sup> and Jan D. Lünemann<sup>1,7</sup>

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- Encouraging case reports
- Gorson et al 2007 no reduction in IVIg requirements in 2 patients
- Dalakas 2010 response in 2/3 patients previously unresponsive to variety of immunosuppressive regimens

## Practical considerations on the use of rituximab in autoimmune neurological disorders

*Ther Adv Neurol Disord*  
Mixalis L. Kosmidis and Marinos C. Dalakas (2010) 3(2) 93–105

# Rituximab in patients with chronic inflammatory demyelinating polyradiculoneuropathy: a report of 13 cases and review of the literature

CIDP

L Benedetti,<sup>1</sup> C Briani,<sup>2</sup> D Franciotta,<sup>3</sup> R Fazio,<sup>4</sup> I Paolasso,<sup>5</sup> C Comi,<sup>6</sup> M Luigetti,<sup>7</sup>  
M Sabatelli,<sup>7</sup> F Giannini,<sup>8</sup> G L Mancardi,<sup>9</sup> A Schenone,<sup>9</sup> E Nobile-Orazio,<sup>10</sup> D Cocito<sup>5</sup>

*J Neurol Neurosurg Psychiatry* 2011;82:306–308.

- 13 patients, all had trialled steroids, IVIg
  - 6/13 previous, 8/13 AZA, 2/13 MMF, 3/13 cyclophos
- Rituximab either because of failure to respond (7/13) or to reduce IVIg dose or PE frequency (6/13)
- 375mg/m<sup>2</sup> IV weekly for 4 weeks
- Neurological assessments at baseline, monthly x6 then 3 monthly
- Before and after NCS for 6 patients
- 9/13 (69%) responded
- Median time to response 2 months after last infusion
- Duration of response up to 1 year
- Of the 7 refractory to other therapy patients 6 improved by at least 4 points on MRC scale and 2 on INCAT
- CD 19+B cells undetectable at 3m, reappeared 6m, back to baseline 9-12m

**Immunomodulatory treatment other than corticosteroids,  
immunoglobulin and plasma exchange for chronic  
inflammatory demyelinating polyradiculoneuropathy (Review)**

Mahdi-Rogers M, van Doorn PA, Hughes RAC

*Cochrane collaboration 2013*

- 4 studies meeting criteria
  - 1 Azathioprine (n=27)
  - 2 IFN b1b (n=77 total)
  - 1 Methotrexate (n=60)
- No significant benefit but problems identified with trials

# Autologous haematopoietic stem cell transplantation: a viable treatment option for CIDP

R Press,<sup>1</sup> H Askmark,<sup>2</sup> A Svenningsson,<sup>3</sup> O Andersen,<sup>4</sup> H W Axelson,<sup>5</sup> U Strömberg,<sup>6</sup> A Wahlin,<sup>7</sup> C Isaksson,<sup>7</sup> J-E J Johansson,<sup>8</sup> H Hägglund<sup>9</sup> *J Neurol Neurosurg Psychiatry* 2014;85:618–624.

- 70-80% CIDP patients respond satisfactorily to first line therapies
- 11 consecutive patients with refractory “typical” CIDP- one with IgMk paraprotein
- Mean follow up 28 m
- 3/11 relapsed (1 re transplanted)
- 8/11 in drug free remission at last follow-up

# Nonmyeloablative AHSCT for CIDP-2014 interim report

Jeffrey Allen University of Minnesota (INC 2014)



- Definite or probable CIDP
- Failed at least 2 line agents
- Harvested with cyclophosphamide and G-CSF
- Conditioning with cyclophosphamide, ATGF, methylprednisolone and rituximab
- 42 patients Jan 2006-April 2014
- 2 deaths from pre-existing conditions
- Drug free remission in 68% at 6m, 75% at 1y, 78% at 3y, 55% at 4y, 40% at 5y
- 40% received immunotherapy at some point after transplant (40% of them in first year and successfully tapered)
- 7 relapses after AHSCT and treatment free interval

# Changing outcome in inflammatory neuropathies

## Rasch-comparative responsiveness

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### ABSTRACT

**Objectives:** We performed responsiveness comparison between the patient-reported Inflammatory Rasch-built Overall Disability Scale (I-RODS) and the widely used clinician-reported Inflammatory Neuropathy Cause and Treatment-Overall Neuropathy Limitation Scale (INCAT-ONLS) in patients with Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and immunoglobulin M-monoclonal gammopathy of undetermined significance related polyneuropathy (IgM-MGUSP).

**Methods:** One hundred thirty-seven patients (GBS: 55, CIDP: 59, IgM-MGUSP: 23) with a new diagnosis or clinical relapse assessed both scales. Patients with GBS/CIDP were examined at 0, 1, 3, 6, and 12 months; patients with IgM-MGUSP at 0, 3, and 12. We subjected all data to Rasch analyses, and calculated for each patient the magnitude of change on both scales using the minimal clinically important difference (MCID) related to the individual standard errors (SEs). A responder was defined as having an MCID-SE  $\geq 1.96$ . Individual scores on both measures were correlated with the EuroQoL thermometer (heuristic responsiveness).

**Results:** The I-RODS showed a significantly higher proportion of meaningful improvement compared with the INCAT-ONLS findings in GBS/CIDP. For IgM-MGUSP, the lack of responsiveness during the 1-year study did not allow a clear separation. Heuristic responsiveness was consistently higher with the I-RODS.

**Conclusion:** The I-RODS more often captures clinically meaningful changes over time, with a greater magnitude of change, compared with the INCAT-ONLS disability scale in patients with GBS and CIDP. The I-RODS offers promise for being a more sensitive measure and its use is therefore suggested in future trials involving patients with GBS and CIDP. *Neurology® 2014;83:1-9*