Place des échanges plasmatiques dans les maladies dysimmunitaires du Système Nerveux Périphérique

Jean-Marc Léger
Centre national de référence maladies neuro-musculaires rares
Institut Hospitalo-Universitaire de Neurosciences

Hôpital de la Salpêtrière and Université Pierre et Marie Curie (Paris VI)

Conflits d'intérêt

- Le Docteur JM Léger a été investigateur, ou conseiller scientifique, ou a participé comme orateur à des réunions organisées par les laboratoires Baxter, Biogen, CSL-Behring, Kedrion, LFB, Novartis, Octapharma, Roche, Serono et Pfizer

Recommandations des agences pour les IgIV et les EP en neurologie

- Immunoglobulines polyvalentes intraveineuses

EMA

Comité d'experts AP-HP

Affsaps/ANSM

- Echanges Plasmatiques

EMA: Note for Guidance on the clinical investigation of IVIg

Substitutive therapy	Immunomodulation
Primary humoral immune deficiencies with hypogammaglobulinemia or agammaglobulinemia :	**Immune thrombocytopenic purpura in children and adults with high risk of bleeding or before surgery**
• **X-linked agammaglobulinemia / constitutive hypogammaglobulinemia** • **Common variable immune deficiency** • **Severe combined immune deficiency** • **Wiskott Aldrich syndrome**	**Guillain-Barré syndrome** **Kawasaki disease**
Multiple myeloma and CLL with severe hypogammaglobulinemia and recurrent infections	

Note for Guidance on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg). The European Agency for the Evaluation of Medicinal Products CPMP/BPWG/388/95 rev. 1

- Addition ?
  - Acute myasthenia gravis Yes ?
  - Chronic inflammatory polyradiculoneuritis Yes ?
  - Multifocal motor polyneuropathy with conduction blocks Yes ?
  - Corticoresistant dermatomyositis No

- Modification ?
  - Secondary immune deficiencies Yes (AB) ?
  - Severe sepsis in neonates No

- Removal ?
  - Bone marrow allograft No

- Addition ?
  - Acute myasthenia gravis Yes ? X
  - Chronic inflammatory polyradiculoneuritis Yes ? X
  - Multifocal motor polyneuropathy with conduction blocks Yes ? X
  - Corticoresistant dermatomyositis No

- Modification ?
  - Secondary immune deficiencies Yes (AB)?
  - Severe sepsis in neonates No X

- Removal ?
  - Bone marrow allograft No

Regional expert group on normal human Ig in 2014

- *President*: L. MOUTHON
- *Physicians*: B.GODEAU, J.E. KAHN, E.OKSENHENDLER, J.M.LEGER, N.MAHLAOUI, C LEGENDRE
- Pharmacists: H. SAUVAGEON, D.DARDELLE, A. LIOU, I. LOPEZ
- *OMEDIT IDF*:M.LE JOUAN, C MONTAGNIER- PETRISSANS
- *COMEDIMS AP-HP*: P.LECHAT

Classification of indications in 4 groups

- *Groupe I:* Authorized (AMM)
- *Groupe II:* Protocoles thérapeutiques temporaires (PTT) ➔ Recommandations temporaires d'utilisation (RTU)
- *Groupe III:* Unacceptable situations
- *Groupe IV:* Clinical situations for which the benefit / risk could not be determined, given the available literature, at the time of the analysis.

Group I (recognized) (II):
Authorized and/or scientifically validated)

- Immunologic thrombocytopenic purpura (ITP) in adults and children in case of important hemorrhage, prevention in case of medical or surgical procedure exposing to an increased risk of hemorrhage and/or to increase the platelet count #
- Kawasaki disease #
- Guillain-Barré Syndrome #
- Motor multifocal polyneuropathy #
- Chronic inflammatory demyelinating polyradiculoneuropathy #
- Birdshot Retinochoroidopathy

AFSSAPS Recommandations for IVIg treatment in tension situation on the French market (I)

	Group 1. Licensed indications (AMM)
Prioritary indication (A)	- PID with defective Ab production, including stem cell transplantation in patients with PID - Kawasaki disease - ITP in children and adults with visceral hemorrhage
Indications reserved to vital emergencies and/or in case of failure of alternative treatment (B)	- Secondary ID with defective Ab production, mainly CLL and multiple myeloma associated with recurrent infections - HIV infection in children with recurrent bacterial infections - Motor multifocal neuropathy - ITP in children and adults - Guillain-Barré syndrome in adults
Non prioritary indications (can wait the end of shortage)	- Birdshot Retinochoroïdopathy

Temporary therapeutic protocols

afssaps
Agence française de sécurité sanitaire des produits de santé

- Acute Myasthenia gravis
- Lambert-Eaton syndrome
- Corticoresistant polymyositis
- Corticoresistant dermatomyositis
- Inclusion body myositis with severe dysphagia
- Miller-Fisher syndrome
- Stiff man syndrome

Neurology

- Prophylaxis of kidney graft rejection in hyperimmunized patients
- Acute rejection in patients undergoing kidney transplantation
- Prophylaxis of acute rejection in patients undergoing kidney transplantation

Kidney transplantation

- Pemphigoid
- Pemphigus
- ANCA-associated vasculitis (first relapse)
- Catastrophic anti-pholpholipid syndrome
- Acquired Willebrand disease

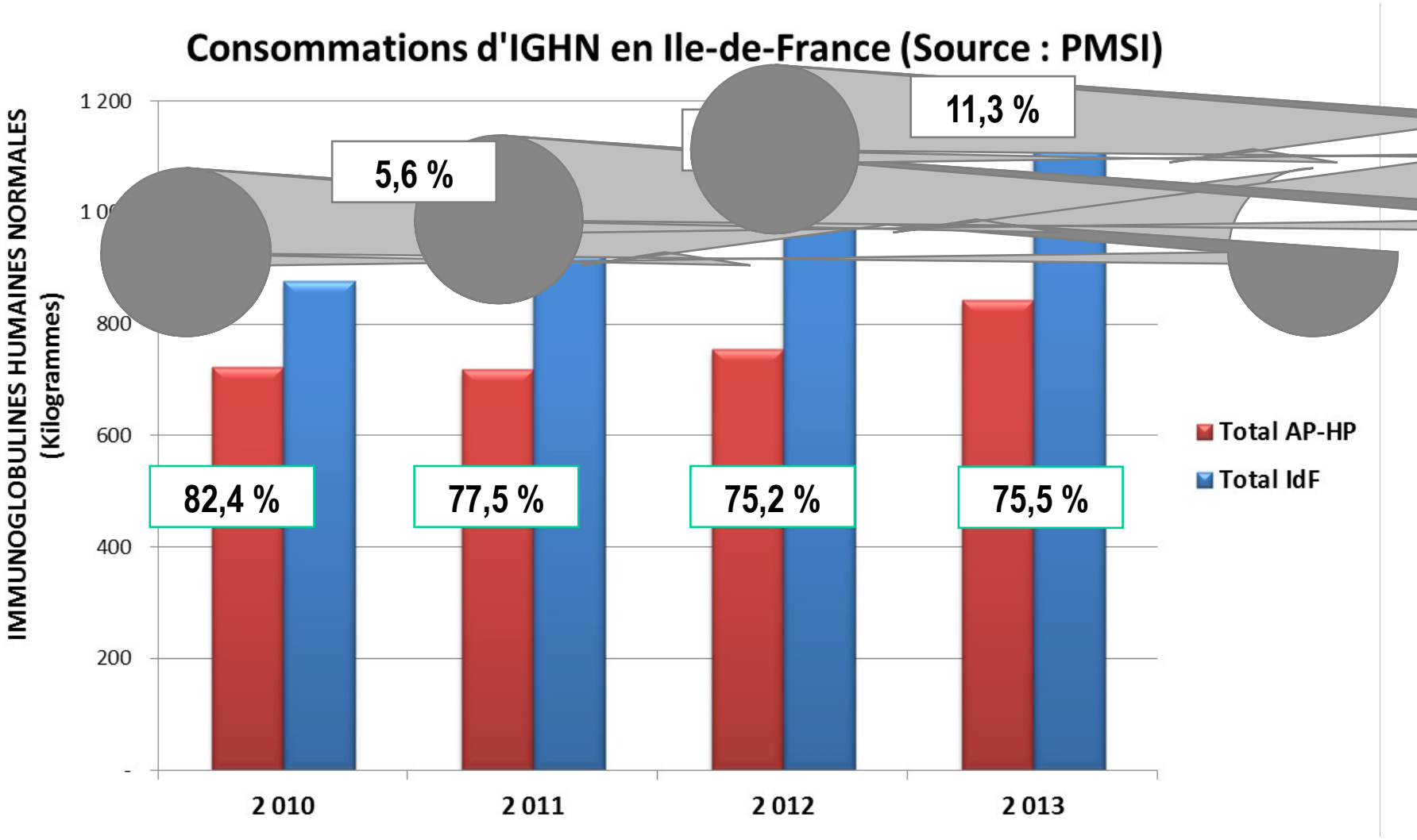
Dermatology

- Prophylaxis of at risk individuals exposed to measles

Other

- Acute or chronic severe parvovirus B19 infections (about to start)
- Prenatal treatment of maternal-fetal alloimmunization specific antiplatelet (anti-HPA) in pregnancy at risk (incompatible fetus).

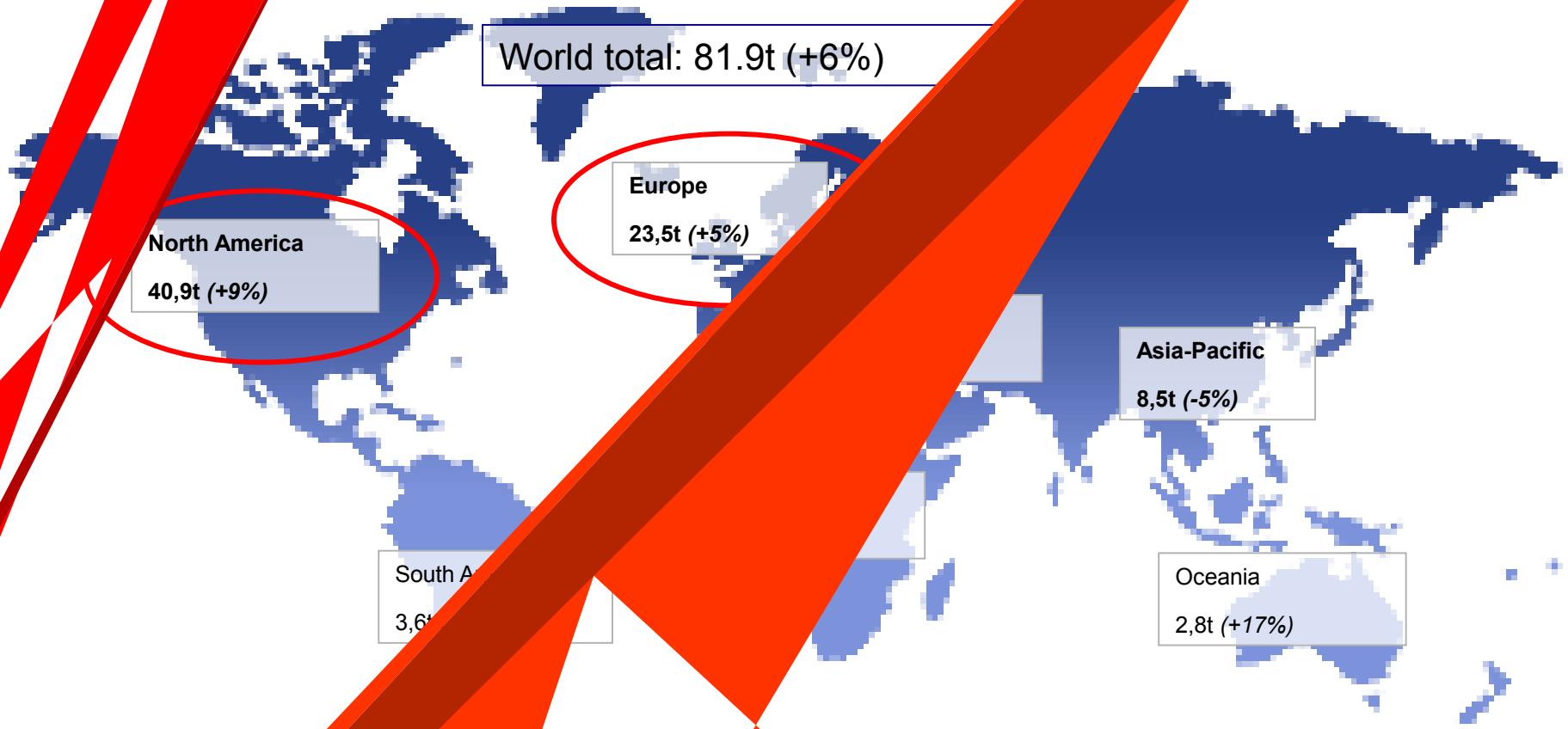
JUSTE PRESCRIPTION. DONNEES QUANTITATIVES – ILE-DE-FRANCE (2)



OMEDIT IDF- M. LEJOUAN- C.MONTAGNIER PETRISSANS- 04/06/2014

Attractivity of USA and Europe (2008)

¾ of IVIg preparations* are prescribed in North America and Europe



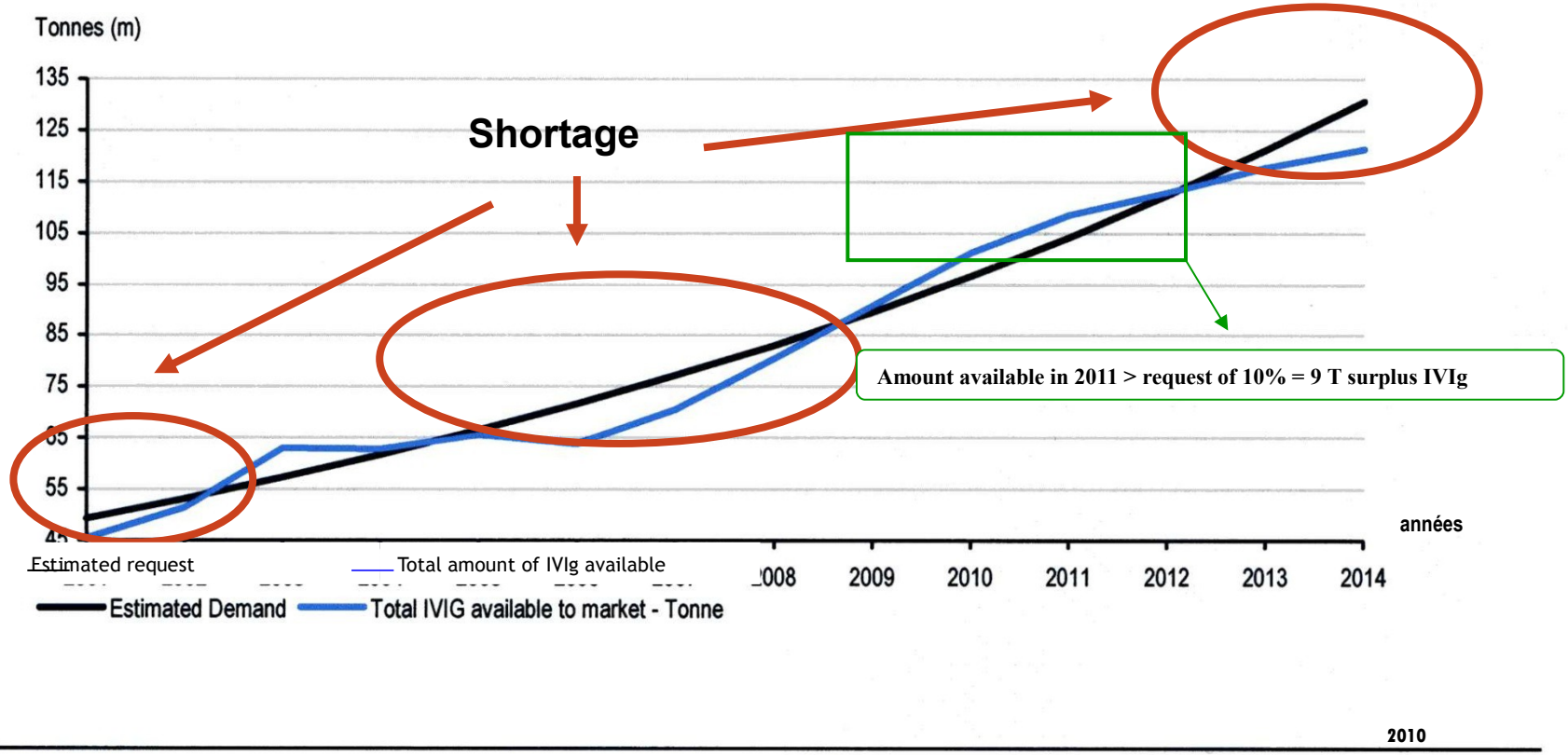
*IVIg: Intravenous immunoglobulins

Source: MF 0, The Worldwide plasma fractions market - 2008

World market for IVIg → alternating periods of shortage and normal supply

Estimation of requests (USA and other countries) and available amounts of IVIg

Chart 3: UBSe UBS global IVIG supply and demand estimates (US and ROW derived IVIG)



2010

Source: MRB, UBS estimates // Note: Examines US & EU derived IVIG vs global demand for US & EU IVIG including ROW demand (global tradable market)

Journal of Clinical Apheresis

The Official Journal of ASFA the American Society for Apheresis

American Society for Apheresis

Volume 28, Number 3, 2013

ASFA 2013 Disease Categories

- Category I
  Apheresis is considered primary or standard therapy.
- Category II
  There is sufficient evidence to suggest efficacy, usually in an adjunctive role.
- Category III
  Insufficient data to determine effectiveness.
  Isolated published studies have indicated that it may be of benefit as a "last-ditch" effort.
- Category IV
  Controlled trials have not shown benefit.

ASFA guidelines – strength of evidence (an example)

ACUTE INFLAMMATORY DEMYELINATING POLYNEUROPATHY (GUILLAIN-BARRÉ SYNDROME)

Incidence: 1–2/100,000/yr	Condition	Procedure	Recommendation	Category
		TPE	Grade 1A	I
	After IVIG+	TPE	Grade 2C	III

# of reported patients*: >300	RCT	CT	CS	CR
	19(1770)	0	9 (369)	10 (11)
After IVIG+	0	0	1(46)	NA

+Completed course of IVIG at 2 g/kg.

Neurology indications for TPE: ASFA 2013

Neurology	Category
Guillan-Barre Syndrome (GBS)	I
Myasthenia Gravis (MG)	I
Paraproteinemic Neuropathies (IgA, IgG, IgM)	I
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	I
Lambert-Eaton Myasthenic Syndrome	II
Voltage Gated Potassium Channel Antibodies (Limbic Encephalitis)	II
Acute disseminated Encephalomyopathy	II
Neuromyelitis Optica (NMO) or Devic's Syndrome	II
Relapsing-remitting Multiple Sclerosis	II
Acute Disseminated Encephalomyelitis	II

Neurology indications for TPE: ASFA 2013

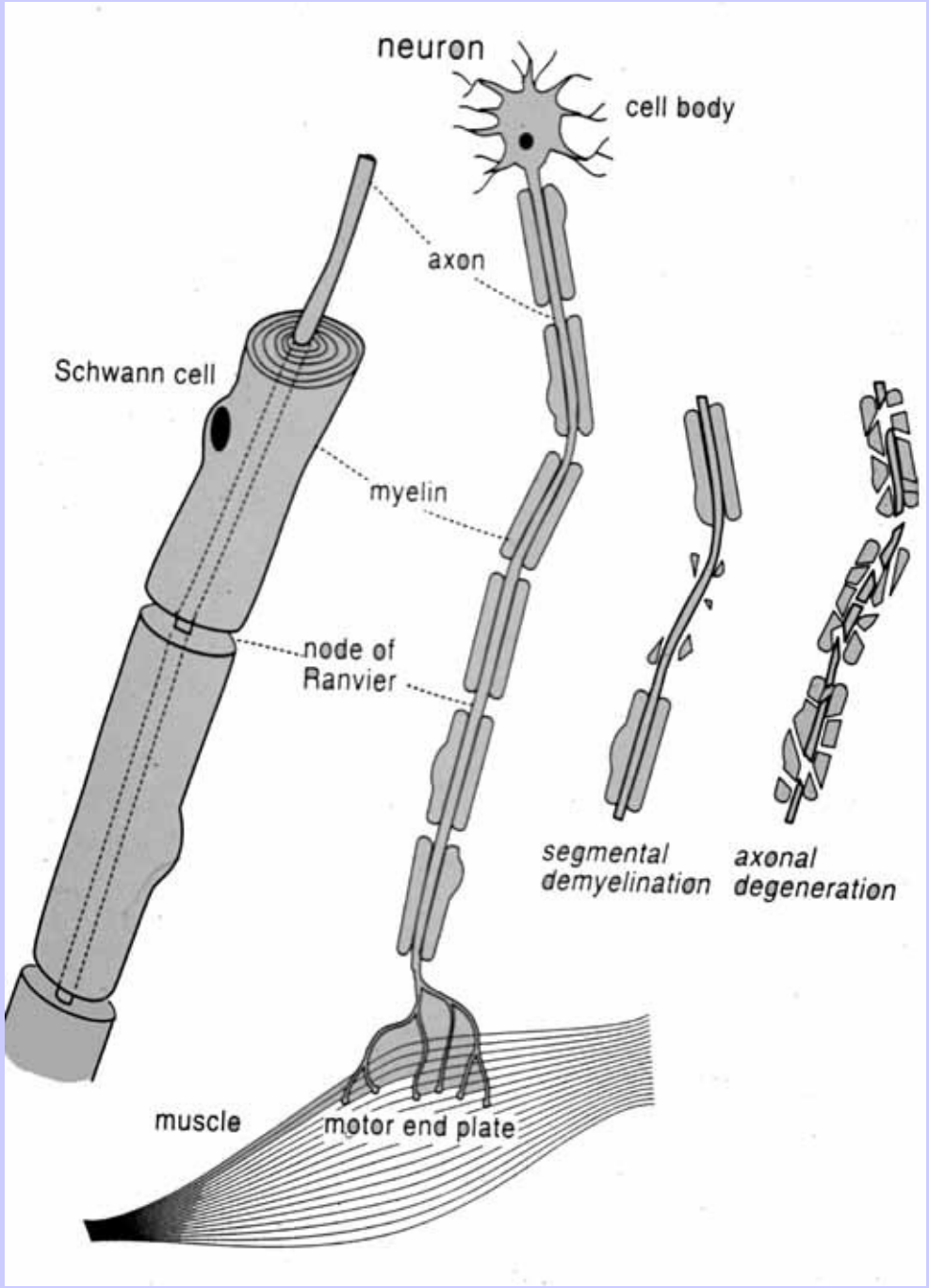
Neurology	Category
Chronic focal encephalitis (Rasmussen Encephalitis)	**III**
Chronic Progressive Multiple Sclerosis	**III**
Monoclonal antibody with PML (Natalizumab removal)	**III**
NMO (TPE maintenance)	**III**
Stiff –person syndrome	**III**
POEMS Syndrome	**IV**

Neurology indications for TPE: Review of Guidelines

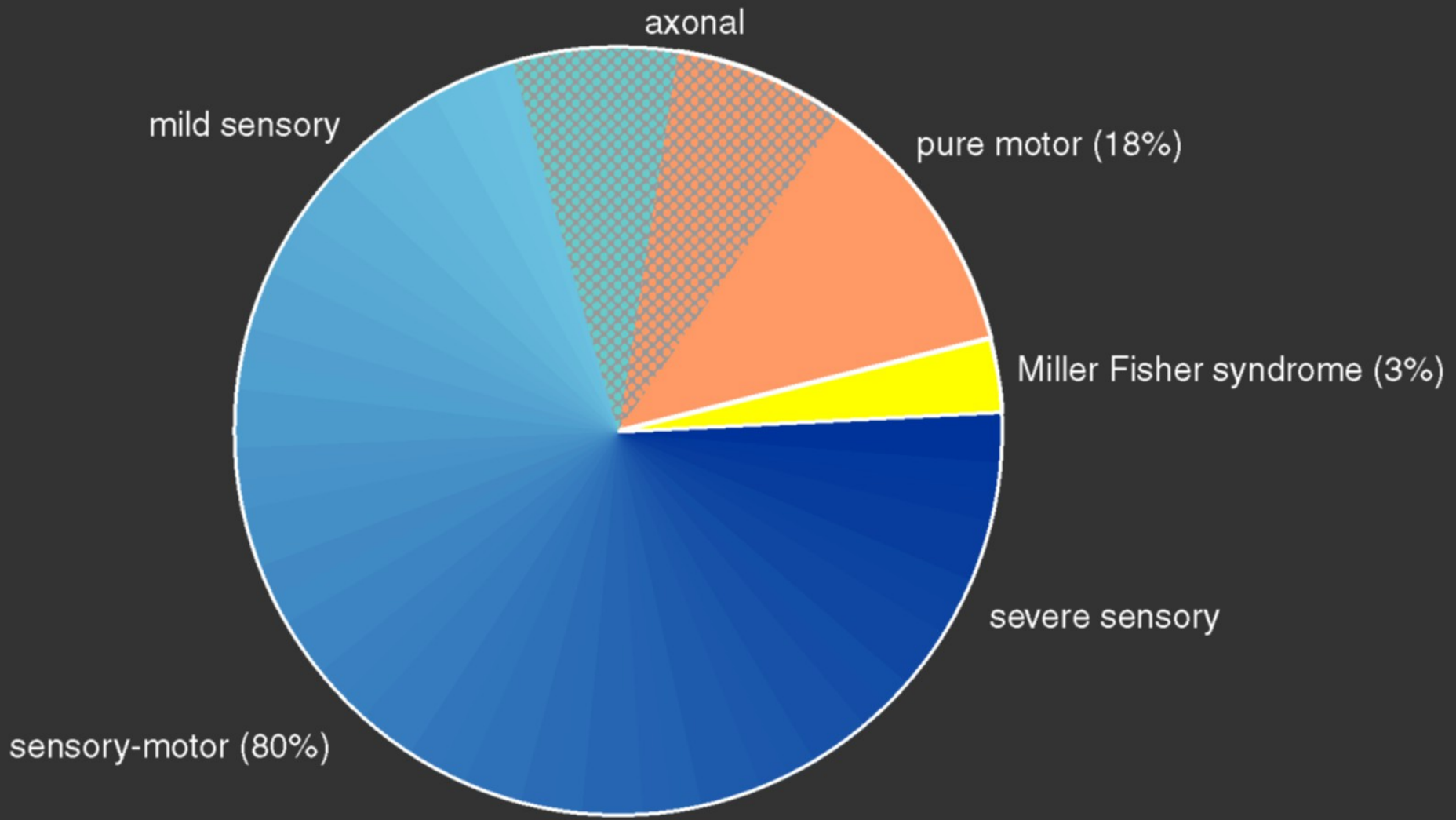
Guillain Barre Syndrome (GBS)	**Category I & Cat. III post IVIG**	**Class I**	**Concurs with AAN**
CIDP	**Category I**	**Class I**	**Concurs with AAN**
Myasthenia Gravis	**Category I**	**Insufficient evidence**	**Concurs with ASFA**
Neuromyelitis Optica	**Category II & Cat. III for maintenance**	**Classified together with MS**	**Concurs with AAN**
Relapses in Multiple Sclerosis	**Category II**	**Class I**	**Concurs with AAN**

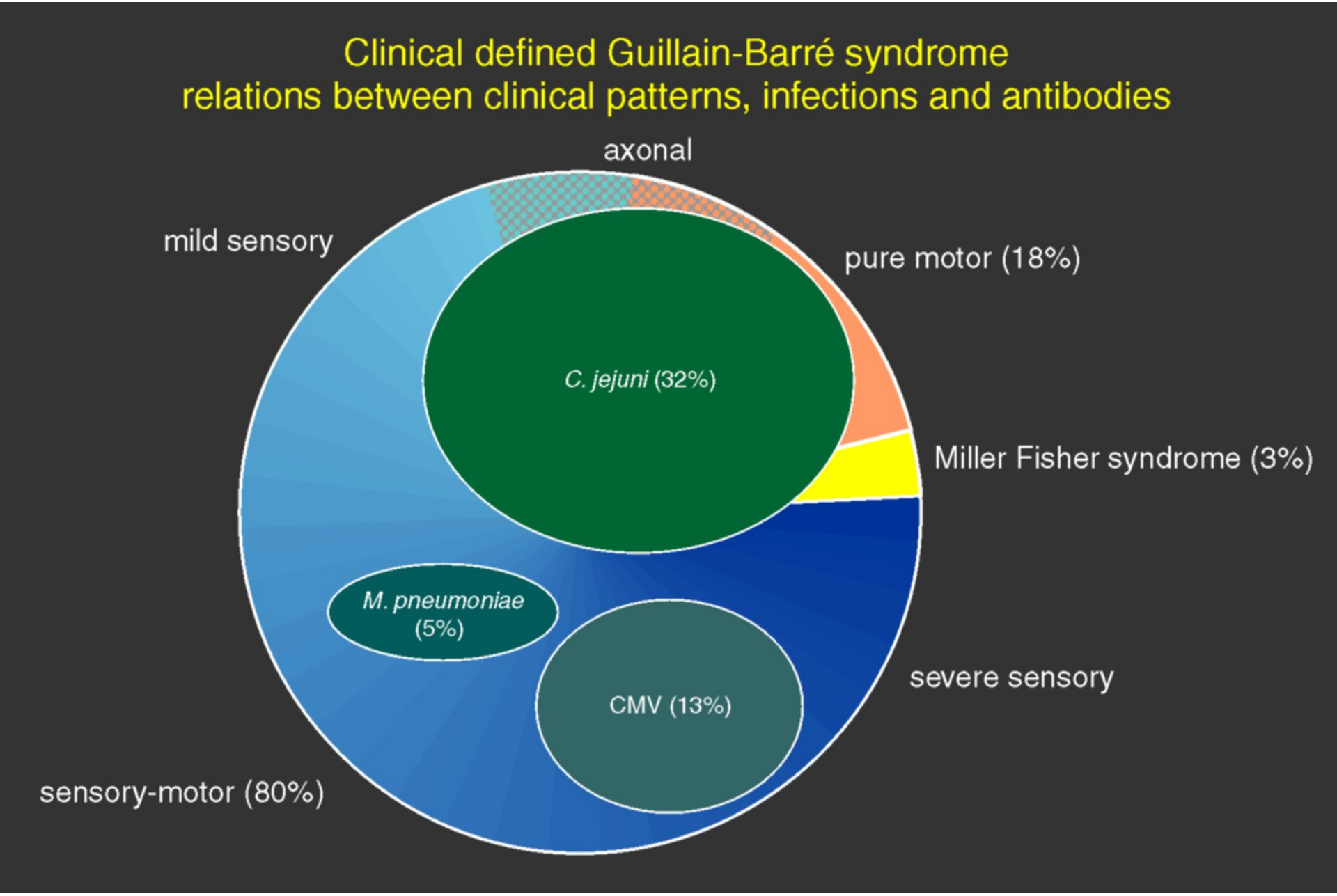
Neuropathies dysimmunitaires

- Syndrome de Guillain-Barré
- Polyneuropathies inflammatoires démyélinisantes chroniques (PIDC)
- Neuropathie motrice multifocale (NMM)
- Polyneuropathie + gammapathie monoclonale (GM) IgM avec activité anti-MAG

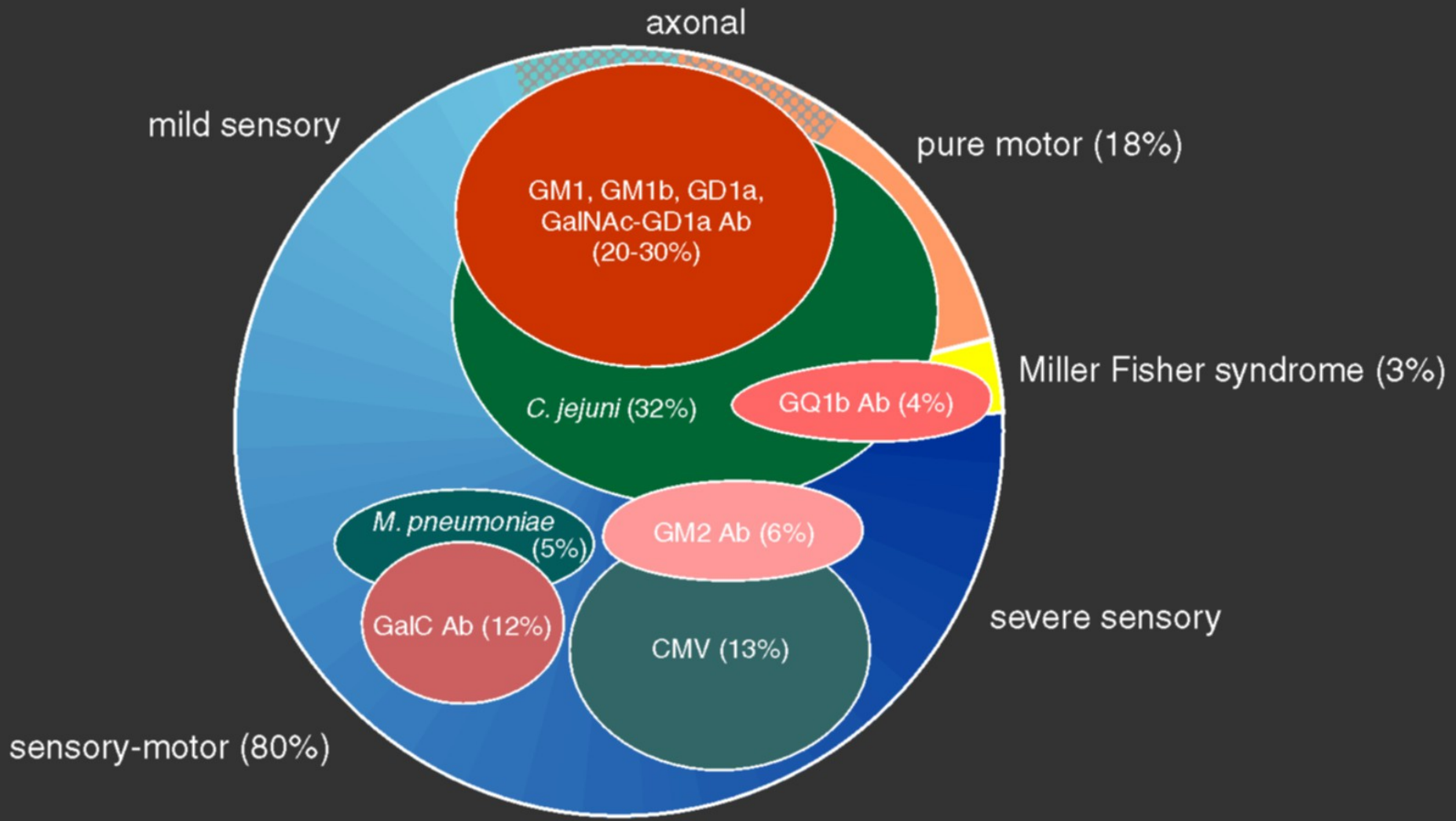

neuron
cell body
axon
Schwann cell
myelin
node of
Ranvier
segmental
demyelination
axonal
degeneration
muscle
motor end plate

Clinical defined Guillain-Barré syndrome
relations between clinical patterns, infections and antibodies




Clinical defined Guillain-Barré syndrome
relations between clinical patterns, infections and antibodies
axonal
mild sensory
pure motor (18%)
C. jejuni (32%)
Miller Fisher syndrome (3%)
M. pneumoniae
(5%)
CMV (13%)
severe sensory
sensory-motor (80%)

Clinical defined Guillain-Barré syndrome
relations between clinical patterns, infections and antibodies



SGB: Données générales

- Prévalence: 1,65-1,79 pour 100.000 aux USA
- Assistance ventilatoire: 25%
- Décès: 5%
- Rechutes: 3%
- Séquelles: 15% (Fatigue persistante: 80%)

Syndrome de Guillain-Barré: traitements de référence

- Corticothérapie seule: échec
- Echanges plasmatiques (EP)

2 EP dans les formes « bénignes », sinon 4

- Immunoglobulines polyvalentes intraveineuses à fortes doses (IgIV)

2g/kg, indication uniquement démontrée dans les formes sévères

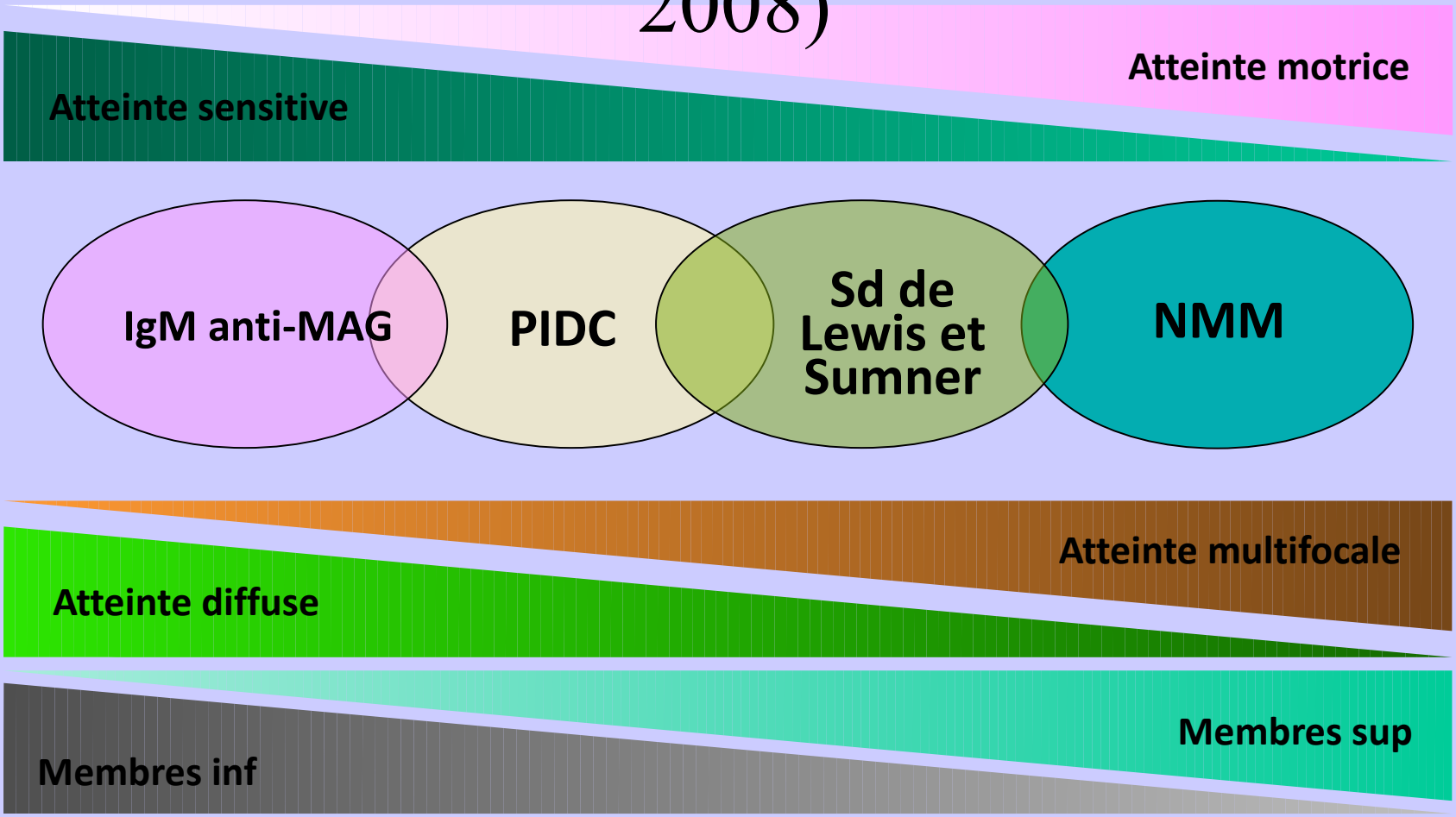
Recommandations AAN (2003)

- Les EP sont recommandés chez les patients non ambulatoires dans les 4 premières semaines et chez les patients ambulatoires dans les 2 premières semaines
- Les IgIV sont recommandées chez les patients non ambulatoires dans les 2 premières semaines. L'efficacité des EP et des IgIV est équivalente
- Les corticoïdes ne sont pas recommandés
- L'association EP suivie d'IgIV n'est pas recommandée (Hughes et al. 1997)

SGB: questions non résolues

- Adaptation des posologies d'IgIV en fonction de la gravité clinique
- Traitement des formes bénignes
- Que faire lorsque le patient ne répond pas à une perfusion d'IgIV 2g/kg ?
- Traitement des rechutes après 1 ou 2 perfusion(s) d'IgIV 2g/kg ?

Spectre clinique des neuropathies dysimmunitaires chroniques (Magy 2008)



Prevalence of CIDP

Studied Area	Population (millions)	Prevalence Mean (range)	M	F
New South Wales	5.995.544	1.9 (1.5-2.2)	2.2	1.6
SE England	3.717.638	1.2 (0.9-1.7)	-	-
Norway	155.464	7.7 (3.2-12.2)	14.7	5
Piémont (Italy)	4.405.669	3 (2.5-3.6)	4.5	1.5

European Journal of Neurology 2006, **13:** 326–332

EFNS TASK FORCE

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

Members of the Task Force: R. A. C. Hughes[a], P. Bouche[b], D. R. Cornblath[c], E. Evers[d], R. D. M. Hadden[a], A. Hahn[e], I. Illa[f], C. L. Koski[g], J. M. Léger[b], E. Nobile-Orazio[h], J. Pollard[i], C. Sommer[j], P. Van den Bergh[k], P. A. van Doorn[l] and I. N. van Schaik[l]

[a]*King's College London School of Medicine, London, UK;* [b]*Consultation de Pathologie Neuromusculaire Groupe Hospitalier, Pitrie-Saltpetriere, France;* [c]*Department of Neurology, John Hopkins University, USA;* [d]*Guillain-Barre syndrome Support Group, LCC offices, Lincolnshire, UK;* [e]*Division of Neurology, London Health Sciences, Canada;* [f]*Servei Neurologica, Hospital Universitari de la Sta Creu I Sant Pau, Barcelona, Spain;* [g]*Department of Neurology, Baltimore, USA;* [h]*Department of Neurology, Milan University, Italy;* [i]*Department of Neurology, University of Sydney, Australia;* [j]*Julius-Maximillians Universitat, Wurzburg, Germany;* [k]*Service de Neurologie, Laboratoire de Biologie Neuromusculaire, Belgium;* [l]*Academic Medical Centre, University of Amsterdam, Netherlands*

First revision: van den Bergh et al. EJN 2010, 17: 356-363

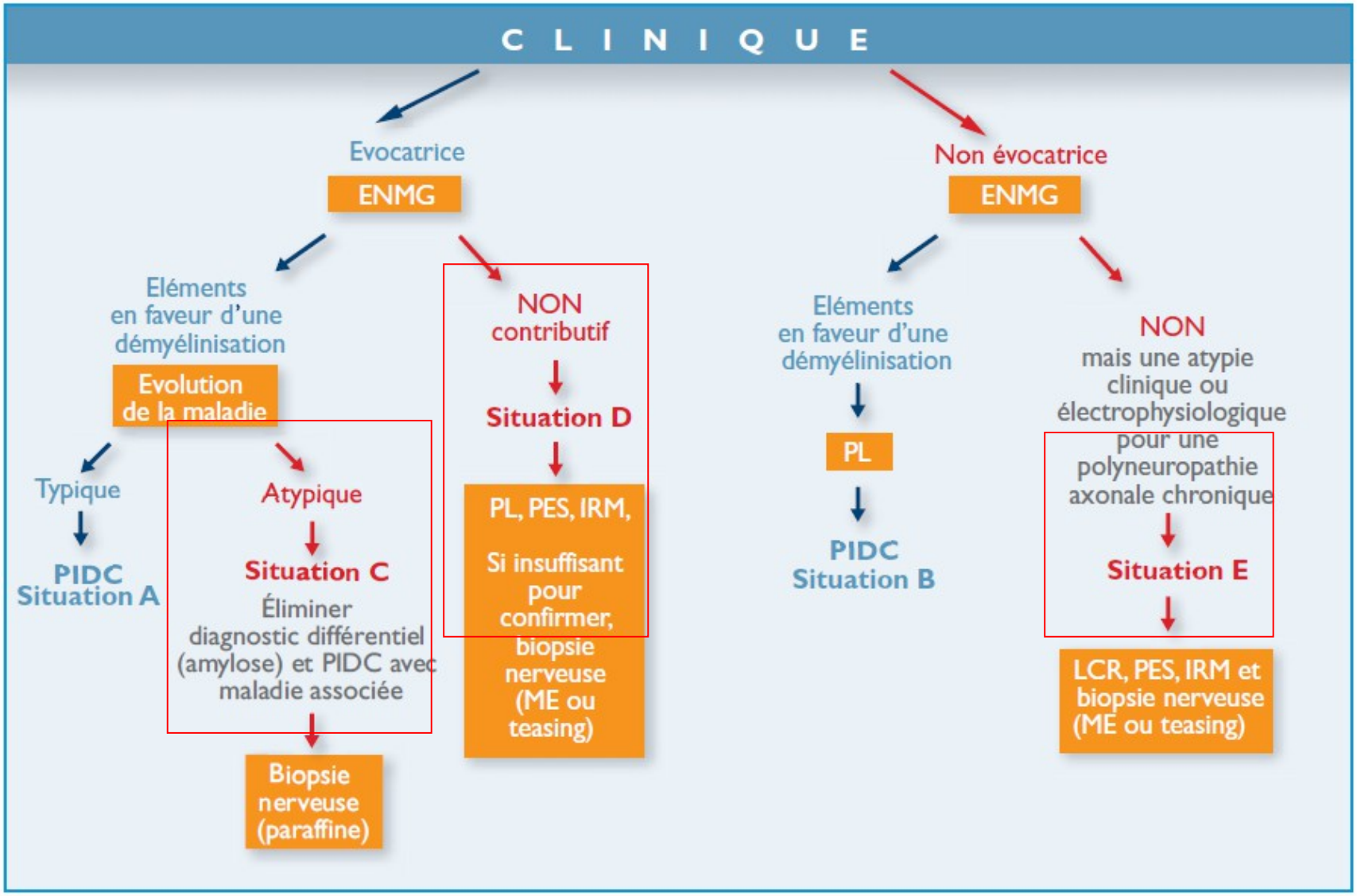
Clinical diagnosis: guideline EFNS/PNS (2010) :Typical CIDP

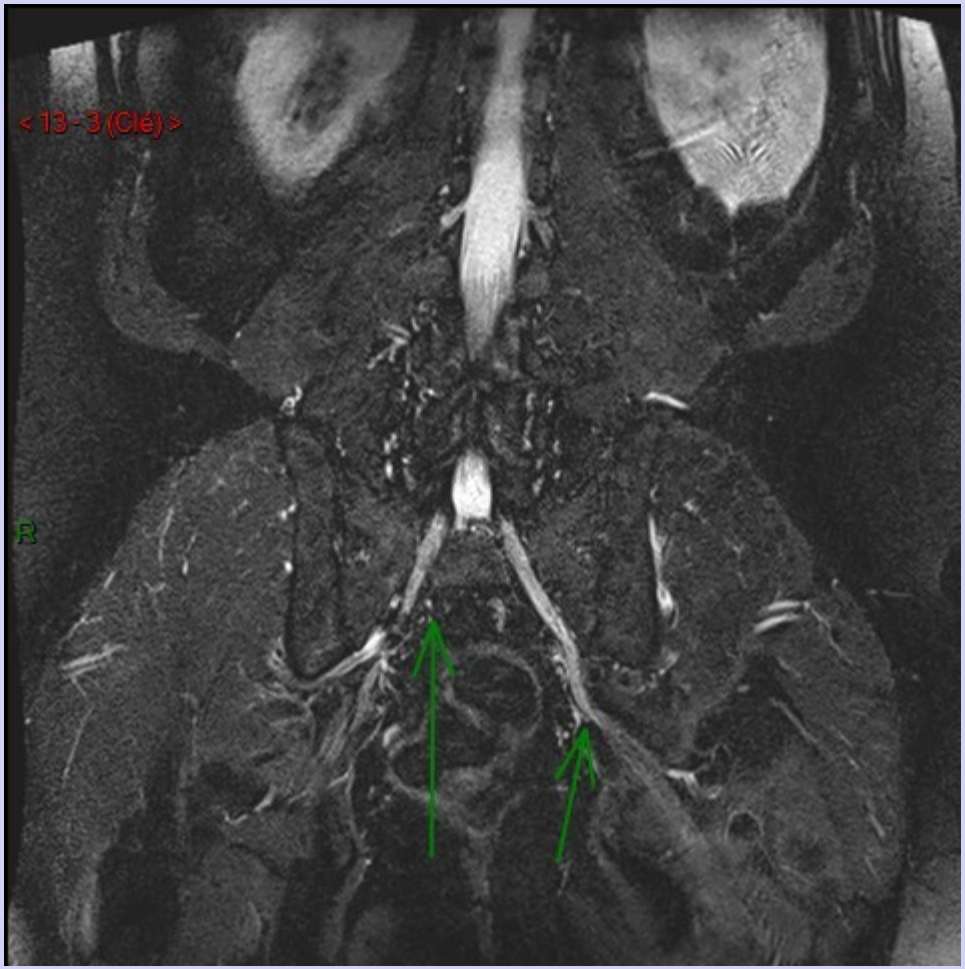
- Chronically progressive, stepwise, or reccurent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected, and
- Absent or reduced tendon reflexes in all extremities

Clinical diagnosis: guideline EFNS/PNS 2010: Atypical CIDP

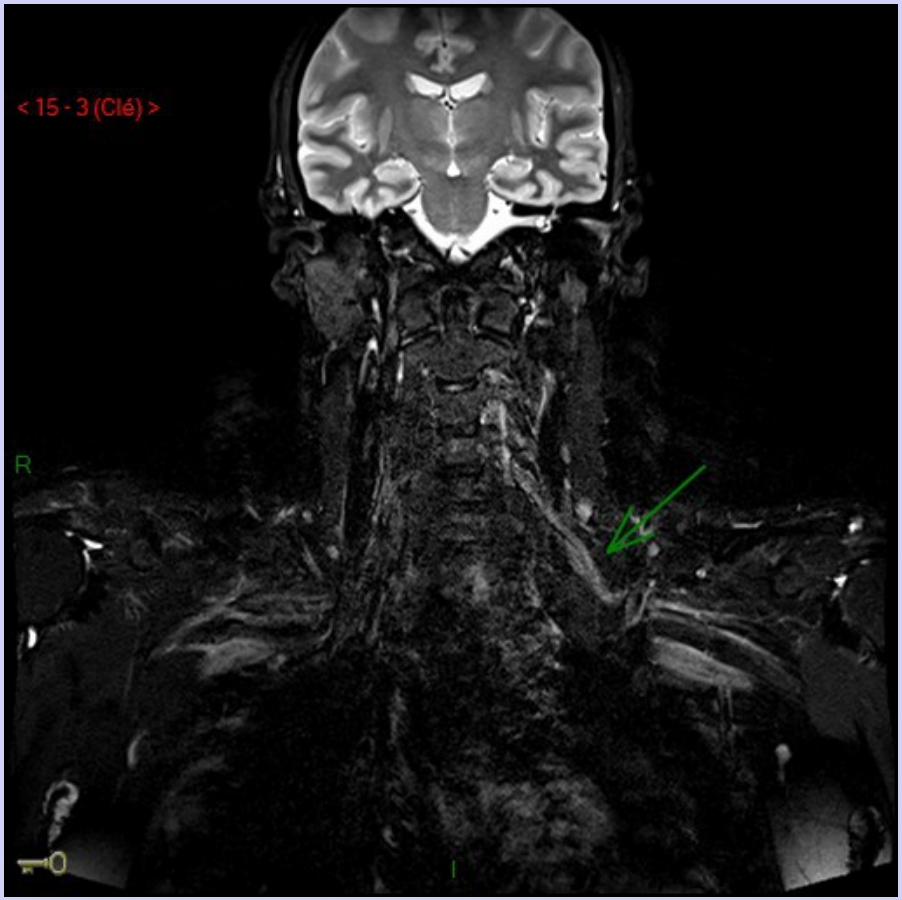
- One of the following, but otherwise as in A
- Predominantly distal weakness (DADS)
- Pure motor or sensory presentations
- Asymetric presentations (LSS)
- Focal presentations (ie involvement of the brachial plexus or 1 or more peripheral nerves in 1 upper limb)
- CNS involvement (may occur with otherwise typical or other forms of atypical CIDP)

Groupe Français d'étude des PIDC: stratégie diagnostique dans les formes atypiques





IRM des plexus lombaires: hypersignaux en T2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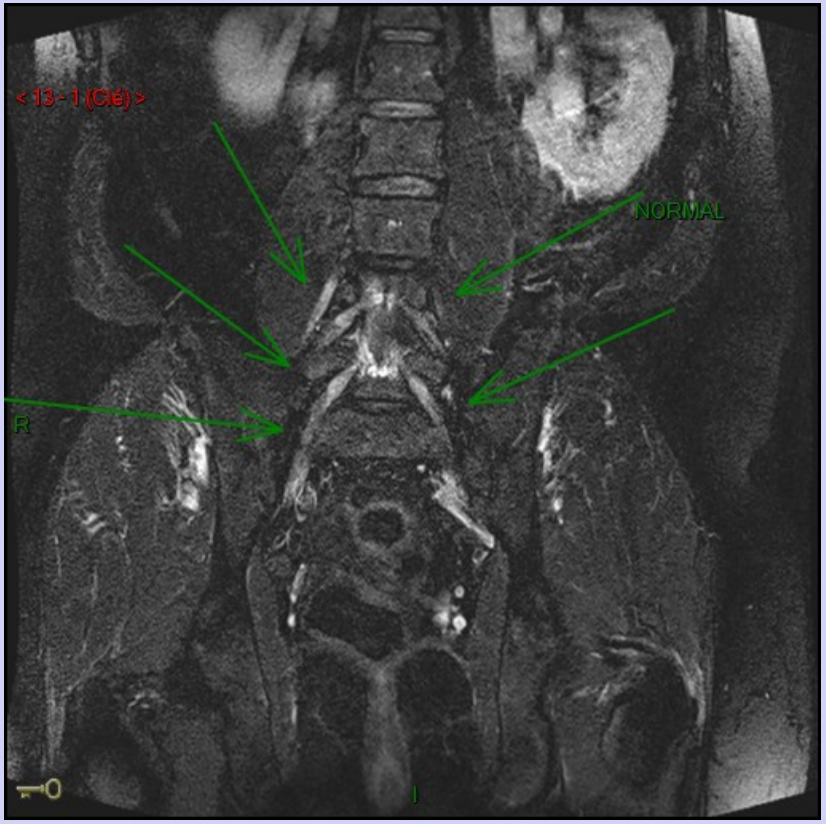
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Available online at www.sciencedirect.com

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Neuromuscular Disorders 23 (2013) 924–933

www.elsevier.com/locate/nmd

Workshop report

196th ENMC international workshop: Outcome measures in inflammatory peripheral neuropathies 8–10 February 2013, Naarden, The Netherlands

Els K. Vanhoutte [a,*], Catharina G. Faber [a], Ingemar S.J. Merkies [a,b], PeriNomS study group [1]

[a] *Maastricht University Medical Centre, Maastricht, The Netherlands*
[b] *Spaarne Hospital, Hoofddorp, The Netherlands*

Overview of the minimum core set, recommendations, and future needs.

	GBS	CIDP	MMN	MGUSP
Minimal core set				
Impairment level	Martin Vigorimeter RT-mISS Being ventilated (Y/N) Duration of ventilation	Martin Vigorimeter RT-mISS 'Manual muscle testing'	Martin Vigorimeter Patient-specific muscle testing RT-MRC scores	Not yet defined; further study required
Activity and participation level	R-ODS GBS disability scale	R-ODS Original INCAT disability score	R-ODS MMN	See above
Quality of life level	–	5-PGIC SF-36	RT-QoL scale	See above
Recommendations				
Impairment level	RT-MRCss Original MRCss RT-FSS	11-PI-NRS RT-FSS	–	RT-mISS
Activity and participation level		–	–	R-ODS Original INCAT 10-point
Quality of life level		–	–	PGIC SF36 or Euro-QoL
Future needs				
Impairment level	Pain Muscle dynamometer/RT-MRCss	RT-MRCss Pain Walking test	–	Define core set Pain Ataxia Tremor 9-hole PEG test
Activity and participation level	Cross-cultural R-ODS	Cross-cultural R-ODS	Expanding the R-ODS	Define core set
Quality of life level	RT-QoL scale	RT-QoL scale	RT-QoL scale	RT-QoL scale

RT, Rasch transformed; mISS, modified INCAT sensory sumscore; R-ODS, Rasch-built overall disability scale; MRCss, Medical Research Council sum score; FSS, fatigue severity scale; 5-PGIC, 5-points patient global impression of change; 11-PI-NRS, 11-point pain-intensity numerical rating scale; QoL, quality of life.

INCAT disability scale

Arm disability

0 = No upper limb problems
1 = Symptoms, in one or both arms, not affecting the ability to perform any of the following functions: doing all zips *and* buttons; washing *or* brushing hair; using a knife and fork together; and handling small coins
2 = Symptoms, in one arm or both arms, affecting but not preventing any of the above-mentioned functions
3 = Symptoms, in one arm or both arms, preventing one or two of the above-mentioned functions
4 = Symptoms, in one arm or both arms, preventing three or all of the functions listed, but some purposeful movements still possible
5 = Inability to use either arm for any purposeful movement

Leg disability

0 = Walking not affected
1 = Walking affected, but walks independently outdoors
2 = Usually uses unilateral support (stick, single crutch, one arm) to walk outdoors
3 = Usually uses bilateral support (sticks, crutches, frame, two arms) to walk outdoors
4 = Usually uses wheelchair to travel outdoors, but able to stand and walk a few steps with help
5 = Restricted to wheelchair, unable to stand and walk a few steps with help

Overall disability = Sum of arm and leg disability

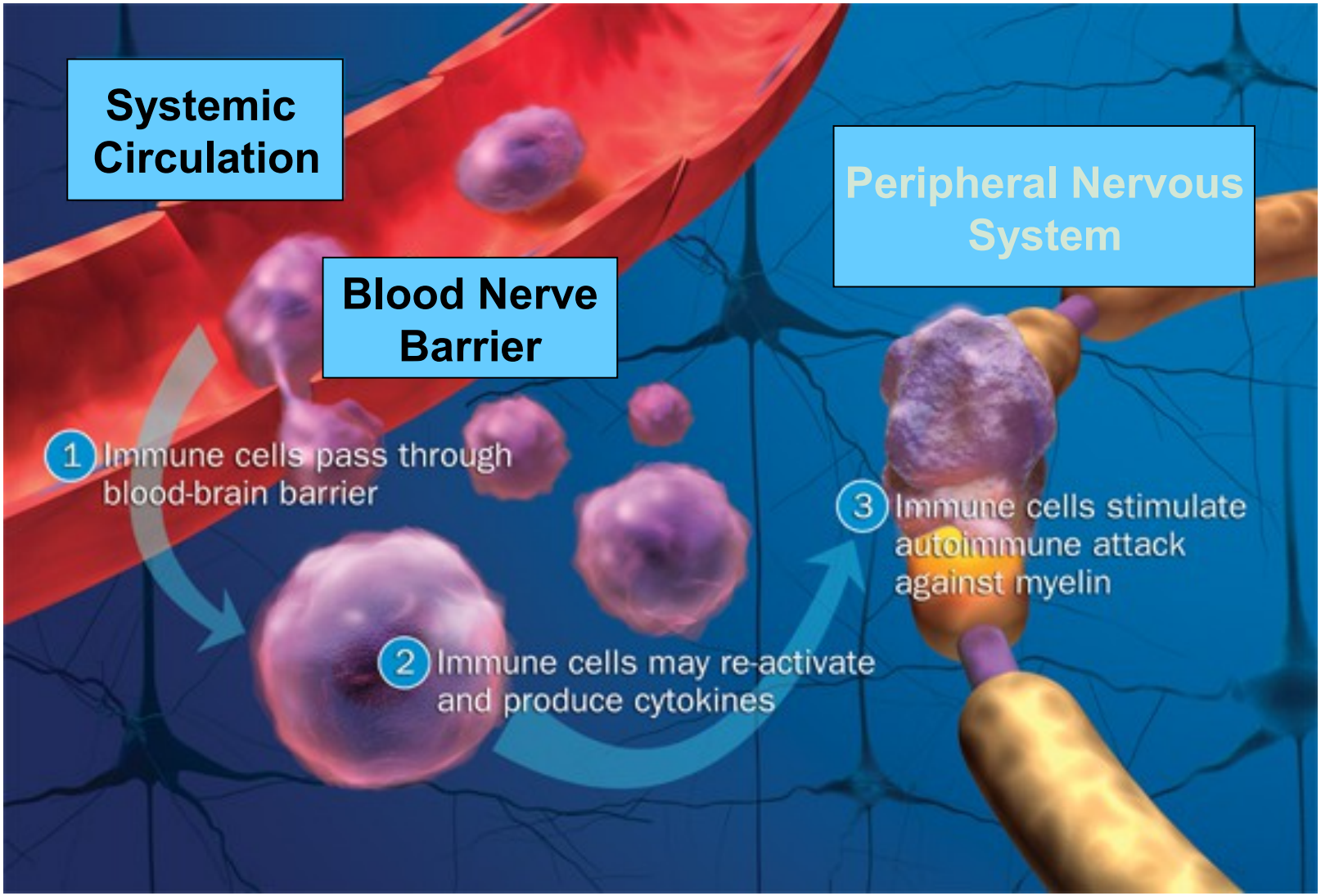
Traitement des neuropathies dysimmunitaires chroniques
Rationnel (1)

- Les neuropathies dysimmunitaires du SNP sont hétérogènes sur le plan clinique
- L'évolution s'effectue de façon progressive ou par « paliers » avec apparition de nouveaux BC
- L'histoire naturelle est imprévisible
- Le pronostic à long terme est conditionné par l'atteinte axonale secondaire

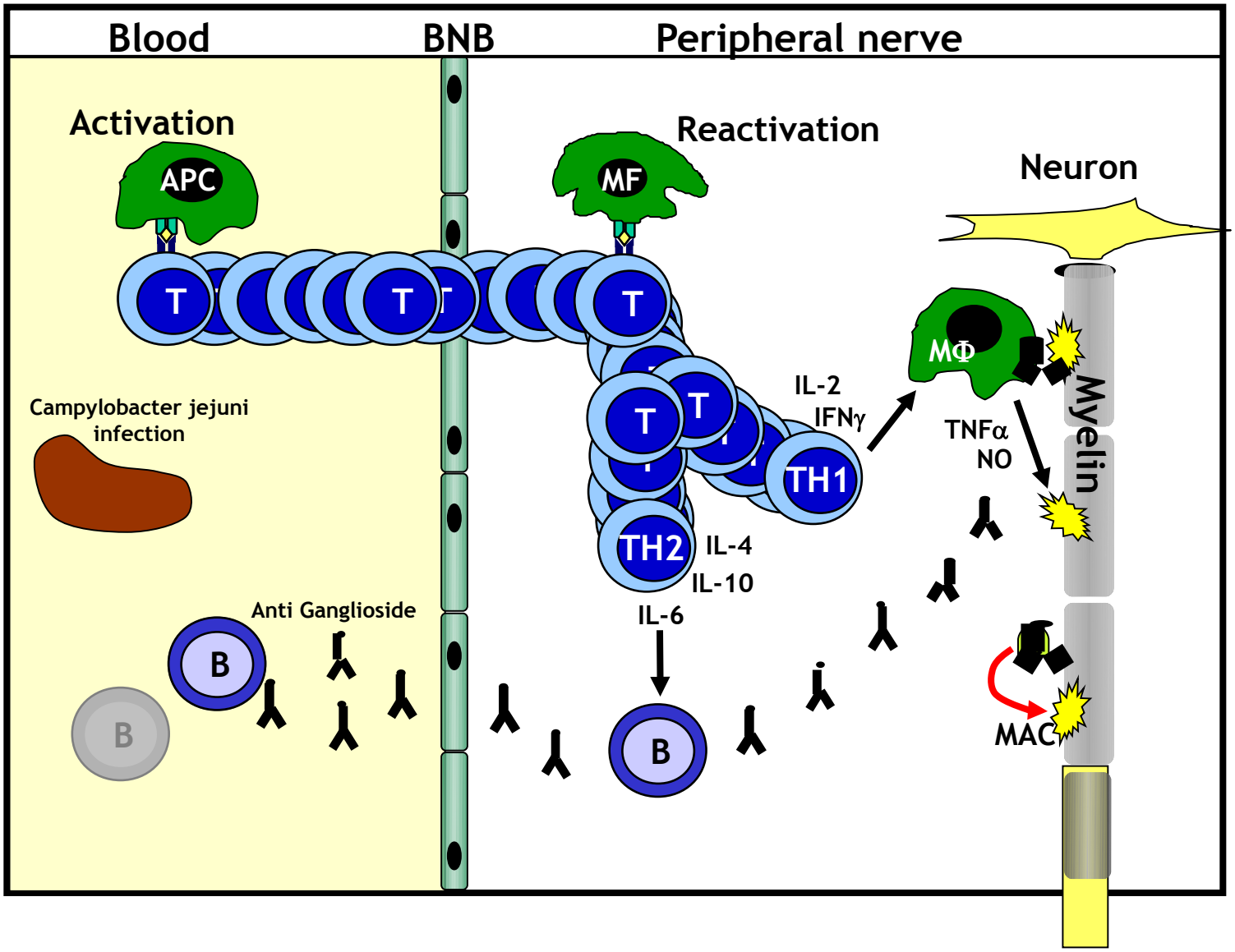
Natural history of CIDP (2)

- In a recent population-based study, nadir overall neuropathy limitation scale score (ONLS) was 5, and 58% of patients were unable to walk independently at some point of their illness. *Mahdi-Rogers and Hughes. Eur J Neurol 2014*
- Between 3% and 7% of patients died during follow-up in another large series. *Maisonobe et al. JNNP 1996*

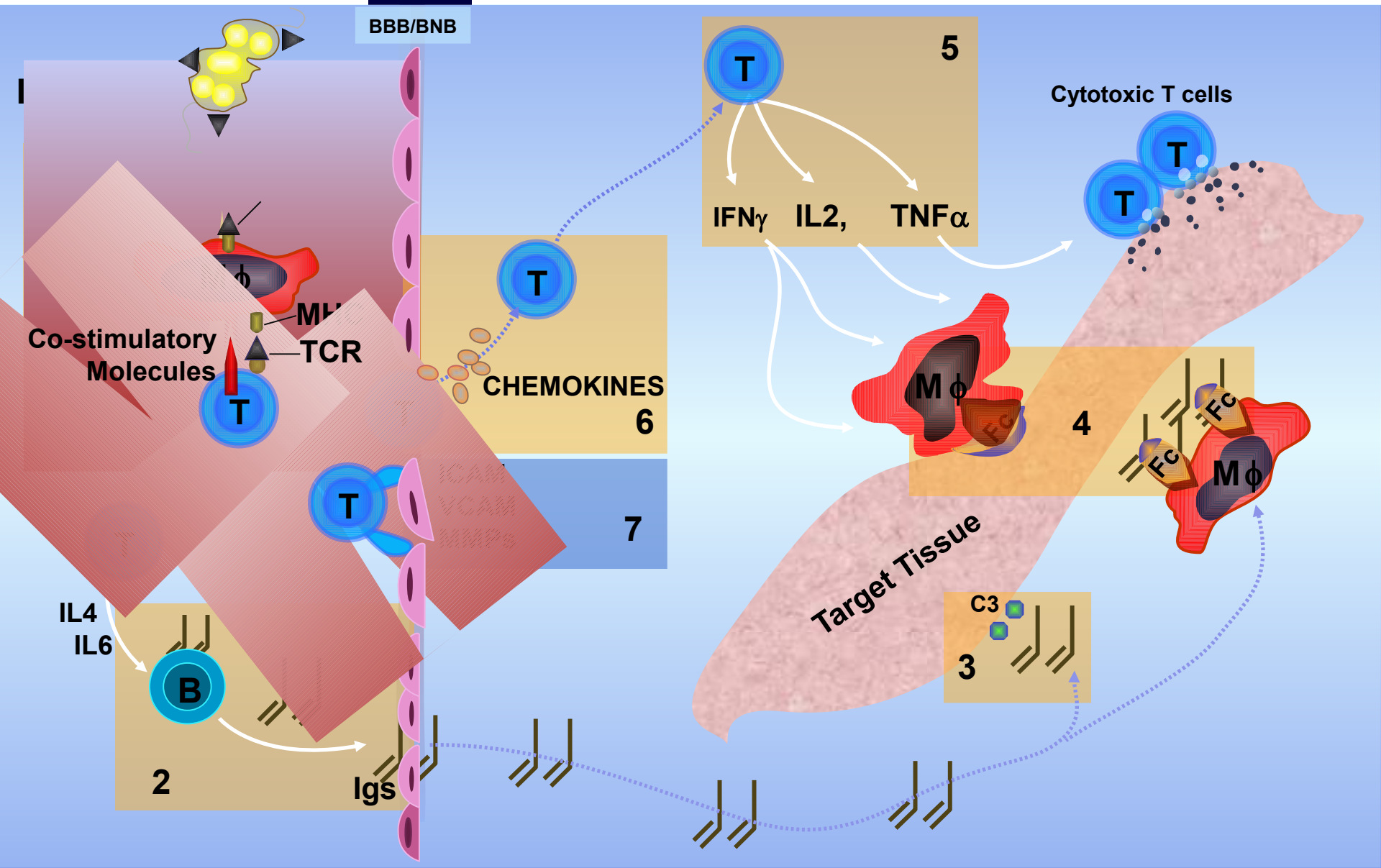
Immune cell trafficking into the PNS



Immune Neuropathies



Targets of Action of Immunotherapeutic Drugs in Autoimmune Neuropathies: Co-stimulatory molecules (1); Antibodies (2); Complement (3); Fc Receptors (4); Cytokines (5); Chemokines (6); Adhesion Molecules (7) [Dalakas MC]



I° Traitements à court terme (* RCT)

- Corticoïdes: 1982*, 1997, 2010*
- Echanges plasmatiques: 1986*, 1996*
- IgIV: 1991, 1996*, 2001*, 2008*

Corticosteroids
(EFNS/PNS Guideline 2010)

- Six weeks of oral prednisolone starting at 60 mg daily produced benefit, that was not significantly different from that of IVIG 2g/kg (Hughes et al. 2001)
- Many observational studies report a beneficial effect from corticosteroids except in pure motor CIDP

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
Published Online
February 3, 2010
DOI:10.1016/S1474-4422(10)70021-1

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 C H 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

Dexamethasone (40 mg/d for 4d x 6 weeks) has the same efficacy that oral prednisolone

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

F. Eftimov, MD
M. Vermeulen, MD, PhD
P.A. van Doorn, MD, PhD
E. Brusse, MD, PhD
I.N. van Schaik, MD, PhD
On behalf of the PREDICT study group

Correspondence & reprint requests to Dr. Eftimov: f.eftimov@erasmusmc.nl

ABSTRACT

Objective: Achieving long-term remission after a limited more intense treatment period would prevent prolonged use of corticosteroids or IV immunoglobulin (IVIg) in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). In this prospective cohort study we present long-term follow-up data on patients included in a multicenter randomized controlled trial comparing 6 monthly pulses of dexamethasone with 9 months of daily prednisolone.

Methods: Treatment effect was assessed with the Inflammatory Neuropathy Cause and Treatment disability scale and the Rivermead Mobility Index and was categorized using the CIDP Disease Activity Status (CDAS) scale.

Results: By March 2011, 39 out of 40 patients were included with a median follow-up of 4.5 years. Cure (>5 years off treatment) or remission according to the CDAS criteria after 1 or 2 courses of pulsed dexamethasone or daily prednisolone was achieved in 10 out of 39 patients (26%). Half of the patients who were in remission after initial treatment experienced a relapse (median treatment-free interval: 17.5 months for dexamethasone, 11 months for prednisolone). Alternative diagnosis was made in 7 out of 12 (58%) who did not respond to any therapy and in none of the treatment-responsive patients.

Conclusions: Cure or long-term remission can be achieved in about one-quarter of patients with CIDP after 1 or 2 courses of pulsed dexamethasone or 9-month daily prednisolone. In treatment-nonresponsive patients, the diagnosis CIDP should be reconsidered.

Classification of Evidence: This study provides Class IV evidence that pulsed dexamethasone or 9-month daily prednisolone can lead to long-term remission in CIDP. *Neurology*® 2012;78:1079-1084

PREDICT Study: long-term follow-up. Eftimov et al. 2012

Long-term remission of CIDP after short-term steroid treatment

- 39 out of 40 of the PREDICT study were included with a mean follow-up of 4.5 years
- Cure (> 5 years off treatment) or remission according to the CDAS criteria, was achieved in 25% of patients after 1 to 2 courses of pulsed dexamethasone, or 8-months daily prednisolone
- Half of the patients who were in remission after initial treatment, experienced relapse after a mean period of 17.5 months for dexamethasone and 11 months for prednisolone

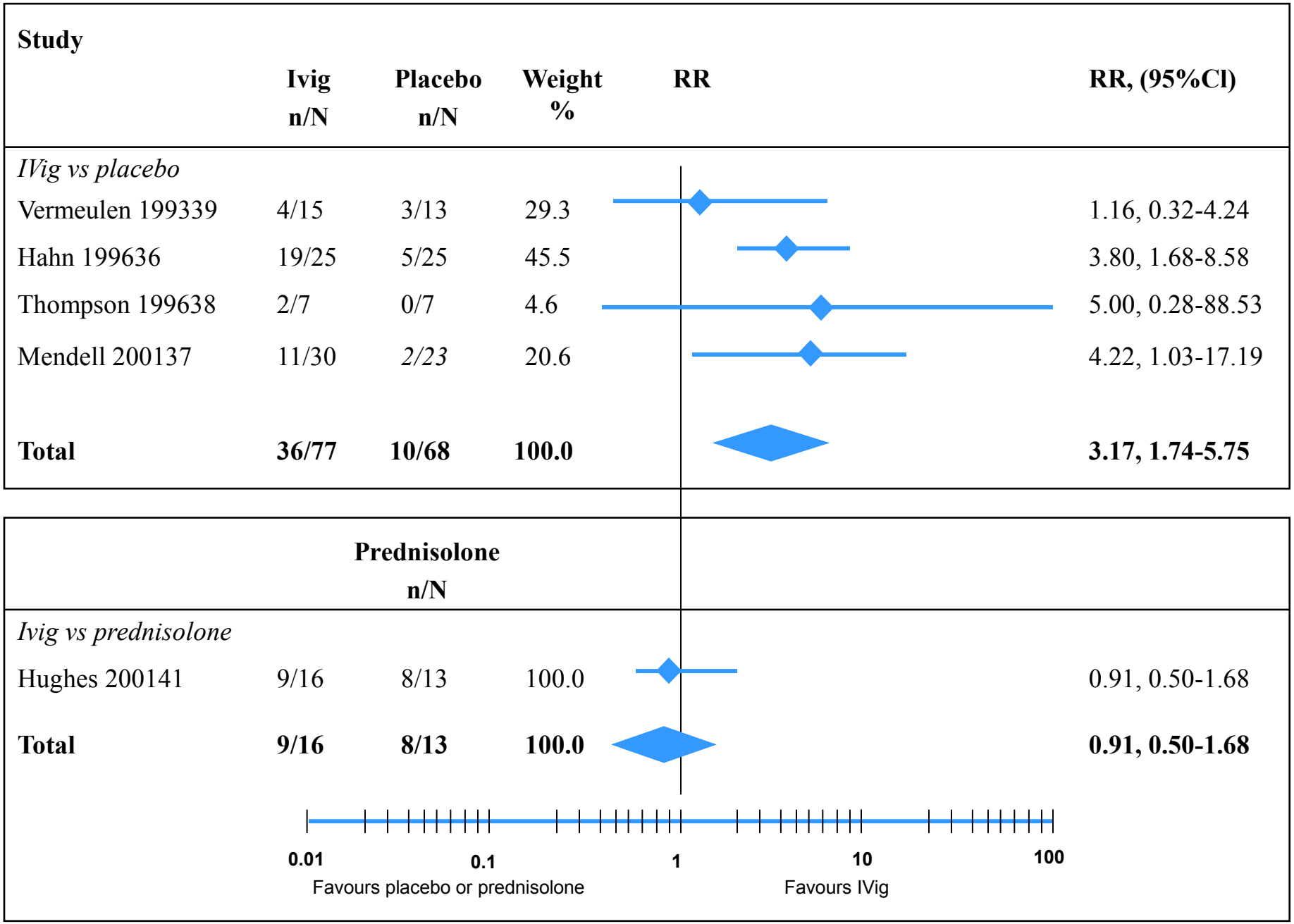
CIDP Disease Activity Status (CDAS)

- 1. Cure: > 5 years off treatment
- 2. Remission: < 5 years off treatment
- 3. Stable active disease: > 1 year on treatment
- 4. Improvement: > 3 months <1 year on treatment
- 5. Unstable active disease: abnormal examination with progressive/relapsing course

Gorson et al. JPNS 2010; 15: 326-33

CIDP: first-line disease modifying therapy (* RCT)

- Corticosteroids: 1982*, 1997, 2010*
- Plasma exchanges: 1986*, 1996*
- IVIg: 1991, 1996*, 2001*, 2008*


Study
Ivig n/N
Placebo n/N
Weight %
RR
RR, (95%CI)
IVig vs placebo
Vermeulen 199339 4/15 3/13 29.3 1.16, 0.32-4.24
Hahn 199636 19/25 5/25 45.5 3.80, 1.68-8.58
Thompson 199638 2/7 0/7 4.6 5.00, 0.28-88.53
Mendell 200137 11/30 2/23 20.6 4.22, 1.03-17.19
Total 36/77 10/68 100.0 3.17, 1.74-5.75
Prednisolone n/N
Ivig vs prednisolone
Hughes 200141 9/16 8/13 100.0 0.91, 0.50-1.68
Total 9/16 8/13 100.0 0.91, 0.50-1.68
0.01
0.1
1
10
100
Favours placebo or prednisolone
Favours IVig

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

*Richard A C Hughes, Peter Donofrio, Vera Bril, Marinos C Dalakas, Chunqin Deng, Kim Hanna, Hans-Peter Hartung, Norman Latov, Ingemar S J Merkies, Pieter A van Doorn, on behalf of the ICE Study Group**

Lancet Neurol 2008; 7: 136–44

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DOI:10.1016/S1474-4422(07)70329-0

See Reflection and Reaction page 115

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Summary

Background Short-term studies suggest that intravenous immunoglobulin might reduce disability caused by chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) but long-term effects have not been shown. We aimed to establish whether 10% caprylate-chromatography purified immune globulin intravenous (IGIV-C) has short-term and long-term benefit in patients with CIDP.

Methods 117 patients with CIDP who met specific neurophysiological inflammatory neuropathy cause and treatment (INCAT) criteria participated in a randomised, double-blind, placebo-controlled, response-conditional crossover trial. IGIV-C (Gamunex) or placebo was given every 3 weeks for up to 24 weeks in an initial treatment period, and patients who did not show an improvement in INCAT disability score of 1 point or more received the alternate treatment in a crossover period. The primary outcome was the percentage of patients who had maintained an improvement from baseline in adjusted INCAT disability score of 1 point or more through to week 24. Patients who showed an improvement and completed 24 weeks of treatment were eligible to be randomly re-assigned in a blinded 24-week extension phase. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00220740.

Findings During the first period, 32 of 59 (54%) patients treated with IGIV-C and 12 of 58 (21%) patients who received placebo had an improvement in adjusted INCAT disability score that was maintained through to week 24 (treatment difference 33·5%, 95% CI 15·4–51·7; p=0·0002). Improvements from baseline to endpoint were also recorded for grip strength in the dominant hand (treatment difference 10·9 kPa, 4·6–17·2; p=0·0008) and the non-dominant hand (8·6 kPa, 2·6–14·6; p=0·005). Results were similar during the crossover period. During the extension phase, participants who continued to receive IGIV-C had a longer time to relapse than did patients treated with placebo (p=0·011). The incidence of serious adverse events per infusion was 0·8% (9/1096) with IGIV-C versus 1·9% (11/575) with placebo. The most common adverse events with IGIV-C were headache, pyrexia, and hypertension.

Interpretation This study, the largest reported trial of any CIDP treatment, shows the short-term and long-term efficacy and safety of IGIV-C and supports use of IGIV-C as a therapy for CIDP.

IVIg CIDP Efficacy (ICE) Trial

- 117 patients CIDP traités 6 mois par IgIV (2g/kg) puis 1g/kg toutes les 3 semaines vs placebo
- Critère primaire: amélioration d'au moins 1 point sur l'échelle INCAT
- IgIV: 32/59 (54%) vs placebo 12/58 (21%) (p=0,0002)
- Période d'extension de 6 mois: moins de rechutes dans le groupe IgIV (13% vs 45%; p=0,011)

CIDP- first-line disease modifying therapy: comparative trials

- Trial comparing PE vs IVIg: Dyck et al. 1994
- IVIg versus prednisolone. Hughes et al. 2001
- IVIg versus IV methylprednisolone (IMC trial) Nobile-Orazio et al. 2012

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, Roberto Macchia, Guido Cavaletti, Fabio Giannini, Mario Sabatelli, for the IMC Trial Group*

Summary

Background Intravenous immunoglobulin (IVIg) and corticosteroids are effective as initial treatment in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), but little is known about the comparative risk–benefit profile of their long-term use in this disease. We compared the efficacy and tolerability of 6-month therapy with IVIg versus that with intravenous methylprednisolone.

Methods We did a multicentre, randomised, double-blind, placebo-controlled, parallel-group study in patients with CIDP. We assessed efficacy and tolerability of IVIg (0·5 g/kg per day for 4 consecutive days) and intravenous methylprednisolone (0·5 g in 250 mL sodium chloride solution per day for 4 consecutive days) given every month for 6 months. Eligible patients had to be in an active or stationary phase of the disease. Allocation to treatments was centrally managed with a computer-generated, 1:1 randomisation scheme with a sequential block size of four. All patients and assessors were unaware of the treatments assignment. After therapy discontinuation, patients were followed up for 6 months to assess relapses. The primary outcome was the difference in the number of patients discontinuing either therapy owing to inefficacy or intolerance. Secondary endpoints included the difference in the proportion of patients experiencing adverse events or worsening after therapy discontinuation. This study is registered with EUDRACT, number 2005-001136-76.

Findings 45 patients (24 IVIg, 21 intravenous methylprednisolone) completed the study; one was excluded for inappropriate inclusion. More patients stopped methylprednisolone (11 [52%] of 21) than IVIg (three [13%] of 24; relative risk 0·54, 95% CI 0·34–0·87; p=0·0085). When adjusted for sex, age, disease duration, comorbidity, modified Rankin scale and ONLS scores at enrolment, and previous treatment with IVIg and steroids, the difference between the two groups remained significant (odds ratio 7·7, 95% CI 1·7–33·9; p=0·0070). Reasons for discontinuation were lack of efficacy (eight in the methylprednisolone group vs three in the IVIg group), adverse events (one in the methylprednisolone group), or voluntary withdrawal (two in the methylprednisolone group). Two patients on IVIg died during follow-up after the 6-month assessment. The proportion of patients with adverse events did not differ between the intravenous methylprednisolone group (14 [67%] of 21) and the IVIg group (11 [46%] of 24; p=0·1606). After therapy discontinuation, more patients on IVIg worsened and required further therapy (eight [38%] of 21) than did those on methylprednisolone (none of ten; p=0·0317).

Interpretation Treatment of CIDP with IVIg for 6 months was less frequently discontinued because of inefficacy, adverse events, or intolerance than was treatment with intravenous methylprednisolone. The longer-term effects of these treatments on the course of CIDP need to be addressed in future studies.

Funding Kedrion.

Lancet Neurol 2012; 11: 493–502

Published Online
May 10, 2012
DOI:10.1016/S1474-4422(12)70057-1

See Comment page 478

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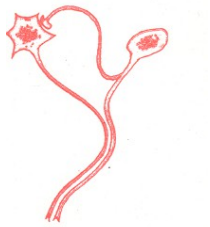
GSSNP

Sponsored by KEDRION

IMC trial: Objectives

- To compare the efficacy & safety of therapy with IVIg (IgVena, Kedrion SpA) or i.v. methylprednisolone (IVMP) for six-months in patients with CIDP
- To compare the rate of relapse in the six-months following therapy suspension

EUDRACT CODE: 2005-001136-76



GSSNP

IMC trial

46 patients with CIDP
(relapsing or progressive)
RANDOMIZATION *

23 patients
Ig 2 g/kg +
MP placebo over 4 days
each month x 6 months

Follow-up for other 6 months for relapse evaluation

September 1, 2007

December 15, 2009

January 31, 2011

23 patients
MP 2 g +
Ig placebo over 4 days
each month x 6 months

Follow-up for other 6 months for relapse evaluation

**** Randomization performed by block of 4 for each participating center***

IMC trial

Primary outcome

- Difference in the proportion of patients suspending treatment during the 6 months of therapy because of side effects, intolerance or inefficacy of therapy (absence of improvement after 2 months *or* worsening by at least 1 point in ONLS after 15 days).

Results II:
Per-group number of failures within 6 mos

	IVMP (n=21)	**IVIg (n=24)**	p-value
	n (%)	*n (%)*	
Success	**10 (47,6)**	**21 (87.5)**	**0.0085**
Failure	**11 (52,4)**	**3 (12.5)**	

Conclusion

- During the 6 months of therapy: more patients on IVMP than on IVIg had to suspend therapy because of inefficacy or adverse events
- After suspension of the 6 months of therapy: more patients treated with IVIg than with IVMP worsened and had to resume therapy

JNNP Online First, published on September 22, 2014 as 10.1136/jnnp-2013-307515

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

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

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ABSTRACT

Background We reported that 6-month therapy with intravenous immunoglobulin (IVIg) was more frequently effective or tolerated than intravenous 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 either of the 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 with 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 in 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.

IMC trial : follow-up

- Percentage of relapses in 41 out of 45 patients included in the IMC trial
- 85.7% in the IVIg group vs 76.9 % in the IVMP group (NS)
- Delay for relapse: 4.5 months in the IVIg group vs 14 months in the IVMP group ($p = 0.0126$)

First-line DMT in CIDP: current status

- Corticosteroids and IVIg have the same efficacy
- IVIg have the best tolerability
- Corticosteroids have a low tolerability, but seem to be followed by greater remission
- Pulsed dexamethasone and IV methylprednisolone may be used in CIDP patients, as they seem to be followed by longer remission than oral prednisolone
- Plasma exchanges are an alternative way in CIDP patients with contra-indications to steroids/IVIg

Long-term prognosis of CIDP: a 5 year follow-up of 38 cases
Kuwabara et al. JNNP 2006; 77: 66-70

- Retrospective study of 38 patients with CIDP
- 89% treated with steroids, 45% with IVIg and 34% with PE: 58% with association
- After 5 years, 10 (26%) had prolonged remission (> 2 years), 23 (61%) partial remision with (26%) or without (34%) other immunomodulator, 5 (13%) had severe disability (unable to walk)
- An overall good response to treatement was associated with symmetric forms, subacute onset, predominantly distal BC and good response to steroids.

Natural history in MS

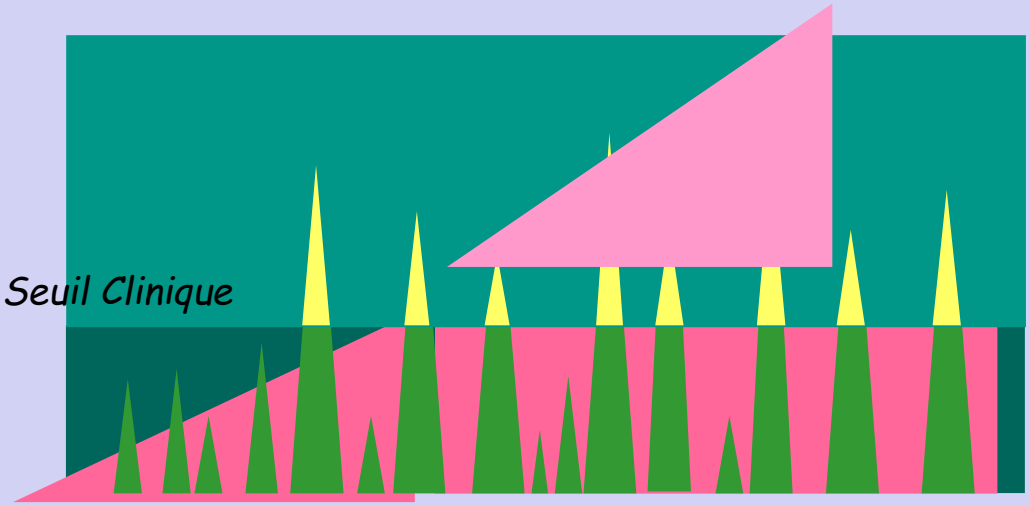
Poussées

> 24 heures

> 1 mois

Prise de Gadolinium

Activité IRM < 1/10



Progression

du Handicap

Irréversible

> 6 mois

"NAWM"

Atrophie Cérébrale

Inflammation

Multifocale

Aigüe, Récurrente

Dégénérescence

Diffuse

Précoce, Chronique,

Progressive

Courtesy: Professor Christian Confavreux

Traitements au long cours

ELSEVIER

Neuromuscular Disorders 18 (2008) 85–89

NMD

www.elsevier.com/locate/nmd

Workshop report

151st ENMC International Workshop: Inflammatory Neuropathy Consortium 13th–15th April 2007, Schiphol, The Netherlands

M.P. Lunn *, J.M. Léger, I.S. Merkies, P. Van den Bergh, I.N. van Schaik, on behalf of the Inflammatory Neuropathy Consortium [1]

Centre for Neuromuscular Disease, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, United Kingdom

Received 29 June 2007

Table 1. Summary of the evidence for the use of immunosuppressant drugs dervived from the Cochrane reviews.

	Mechanism	Cost	Evidence		Safety
			CIDP	MMN	
Cyclophosphamide	broad	+	+	+	---
Azathioprine	broad	+	+	?	--
Methotrexate	broad	+	0	0	-
Ciclosporin	broad	++	+	0	--
Mycophenolate	lymphocyte	++	+	?	-
Rituximab	B cell	+++	?	+	-
Beta interferon 1a	broad	+++	+	+	-
Alpha interferon	broad	+++	+	0	-
Etanercept	T cell	+++	?	0	-

Interferon beta-1a as an investigational treatment for CIDP

J.-M. Vallat, MD; A.F. Hahn, MD; J.-M. Léger, MD; D.P. Cros, MD; L. Magy, MD; F. Tabaraud, MD; P. Bouche, MD; P.-M. Preux, MD, PhD

- Phase II multicentric trial with Avonex IM, 30 microgrammes once/a week, 6 months
- Good tolerability (as in MS)
- Résults: 7 patients (35%) improved on NDS, clinical grading scale and grip strength, 10 patients (50%) were stable and 3 (15%) worsened

Neurology 2003; 60 (Suppl 3): S23-S28

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Intramuscular interferon beta-1a in chronic inflammatory demyelinating polyradiculoneuropathy

Neurology 2010;74;651-657
DOI: 10.1212/WNL.0b013e3181d1a862

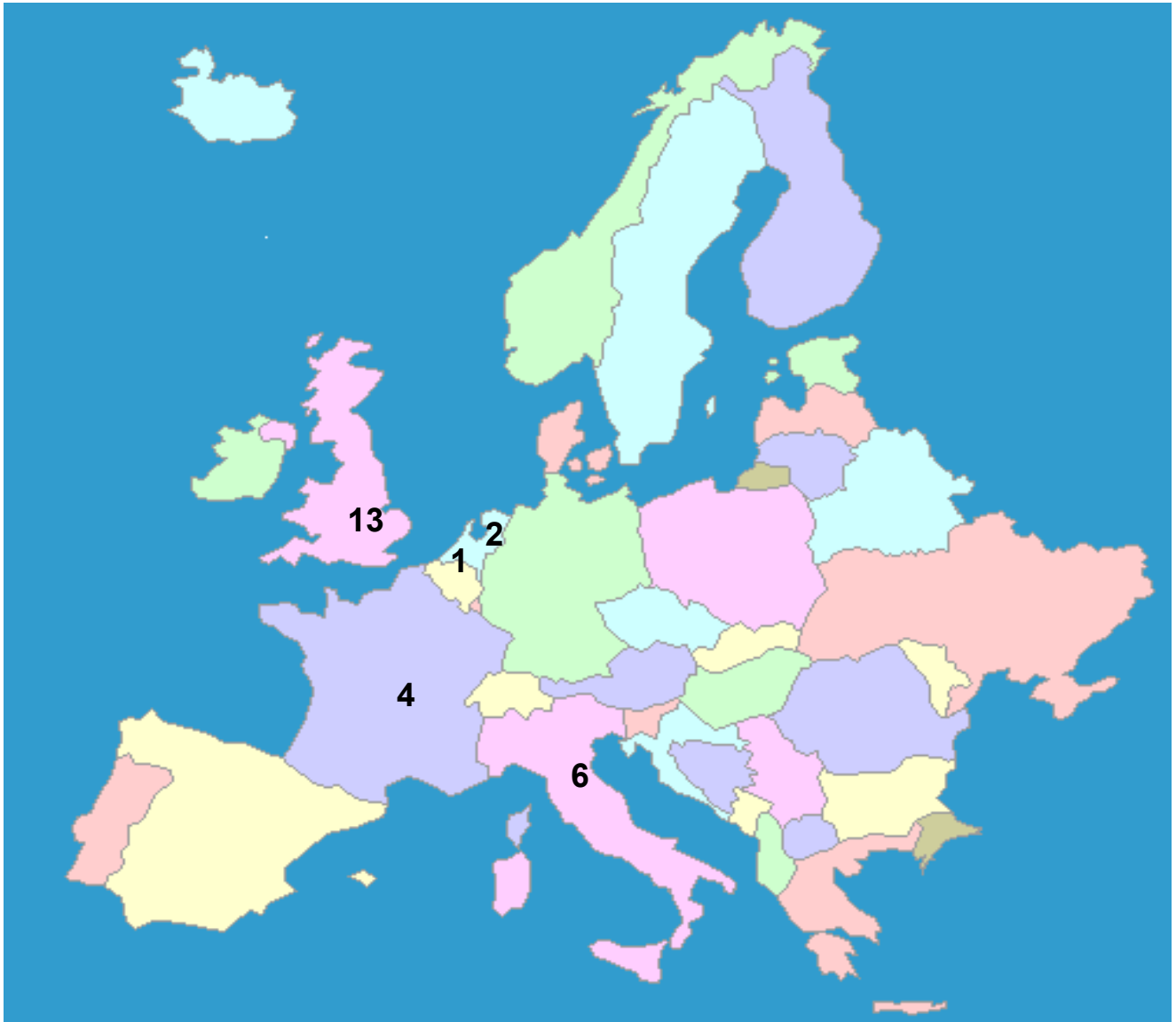
Bêta-1a interferon has no efficacy as adjuntive therapy during 6 months

RMC Trial

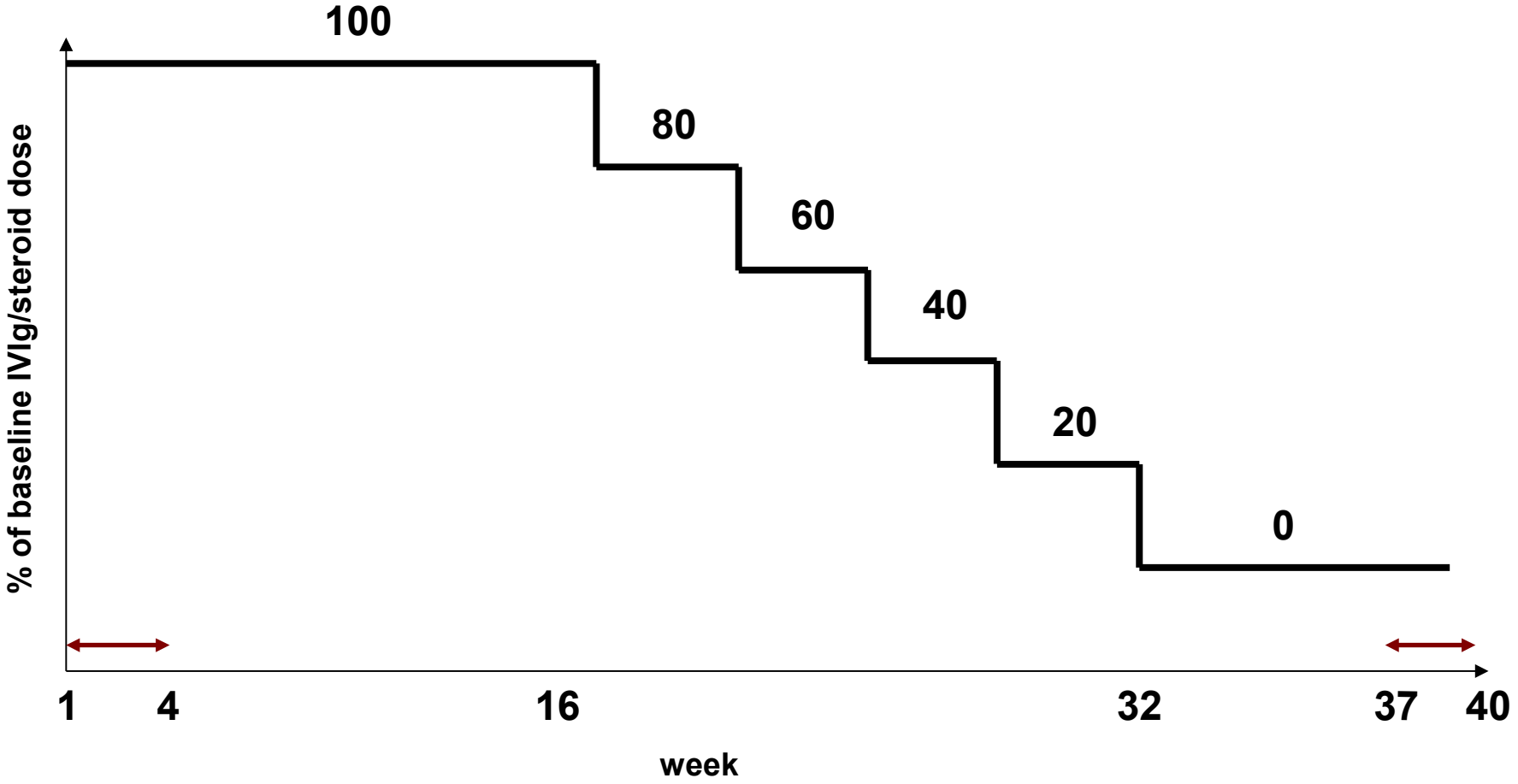
A Pilot Randomised controlled trial of Methotrexate for Chronic Inflammatory Demyelinating Polyradiculoneuropathy

M Mahdi Rogers

RMC Trial Centres



Trial Design



7.5 → 10 → 15 →

Methotrexate mg/week

Descriptive statistics

- 59 of 60 recruited were present in the final analysis
- There were a slightly higher proportion of responders in methotrexate 52% vs. 44% in placebo

Responder	Placebo	Methotrexate	Total
No	18 (56%)	13 (48%)	31(53%)
Yes	**14 (44%)**	**14 (52%)**	**28 (47%)**
Total	32 (100%)	27 (100%)	59 (100%)

European Journal of Neurology 2011, 18: 1417–1421 doi:10.1111/j.1468-1331.2011.03495.x

Immunosuppressive treatment in refractory chronic inflammatory demyelinating polyradiculoneuropathy. A nationwide retrospective analysis

D. Cocito[a], S. Grimaldi[a], I. Paolasso[a], Y. Falcone[a], G. Antonini[b], L. Benedetti[c], C. Briani[d], R. Fazio[e], S. Jann[f], S. Matà[g], M. Sabatelli[h] and E. Nobile-Orazio[i] On behalf of The Italian Network for CIDP Register*

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110 pts with « refractory CIDP » followed in 10 centers and treated with IS:
77 pts: azathioprine, 18: rituximab, 13: CTX, 12: mycophenolate mofétil,
12: ciclosporine, 12: MTX, 11: IF alpha, 3: IF bêta-1a
The percentage of responders to azathioprine (27%) was similar to that observed with the other IS, except IF bêta-1a (not efficacious)
Side effects more marked with ciclosporine and the lowest with MTX

NMM: Arguments du diagnostic

- Signes cliniques
- Signes électrophysiologiques
- Présence d'anticorps sériques de classe IgM dirigés contre le ganglioside GM1

NMM: signes cliniques

- Rare (0.1 à 0.2 pour 100.000)
- Prédominance masculine (sexe-ratio: 2,6:1)
- Débutant dans 80% des cas entre 20 et 50 ans (moyenne 41,4)
- Atteinte multifocale motrice pure débutant et prédominant aux membres supérieurs
- Aggravation par le froid

Traitements disponibles

- Contrairement à ce qui est observé dans les PIDC, les corticoïdes et les échanges plasmatiques sont inefficaces et parfois délétères
- Un seul traitement immunomodulateur a été rapporté comme efficace: les Immunoglobulines polyvalentes à fortes doses par voie intraveineuse (IgIV)

Myasthénie: Traitement à court terme : échanges plasmatiques et IgIV

- EP
  2 ou 3 sur une semaine

- IgIV : 1 à 2 g/kg par cure.

Effet rapide (quelques jours), mais transitoire (quelques semaines)

Association systématique à un traitement de fond (thymectomie, corticoïdes, immunosuppresseurs)

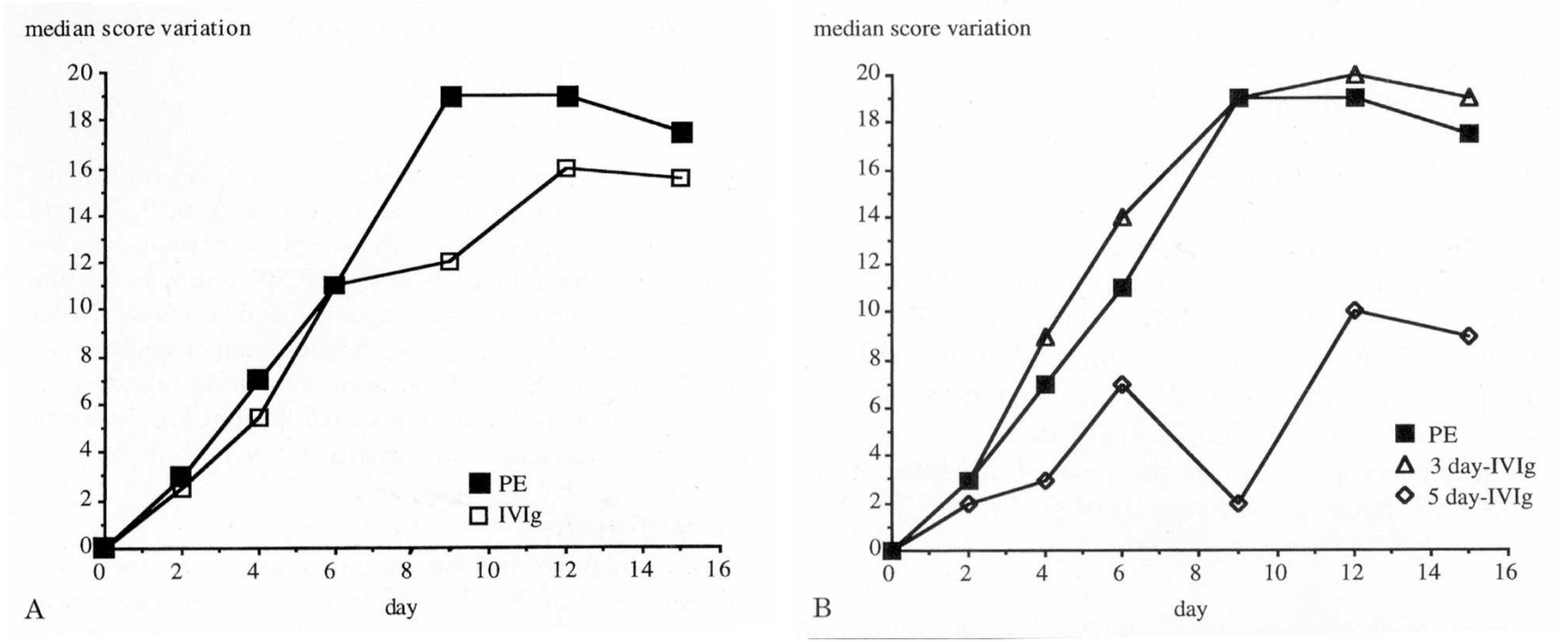
Echanges plasmatiques et IgIV

même efficacité ?

même tolérance ?

Comparaison des échanges plasmatiques et des IgIV dans la myasthénie

Gajdos et al, 1997



Evolution du score myasthénique : effet identique

.

Comparaison EP et IgIV dans la myasthénie Gajdos et al, 1997

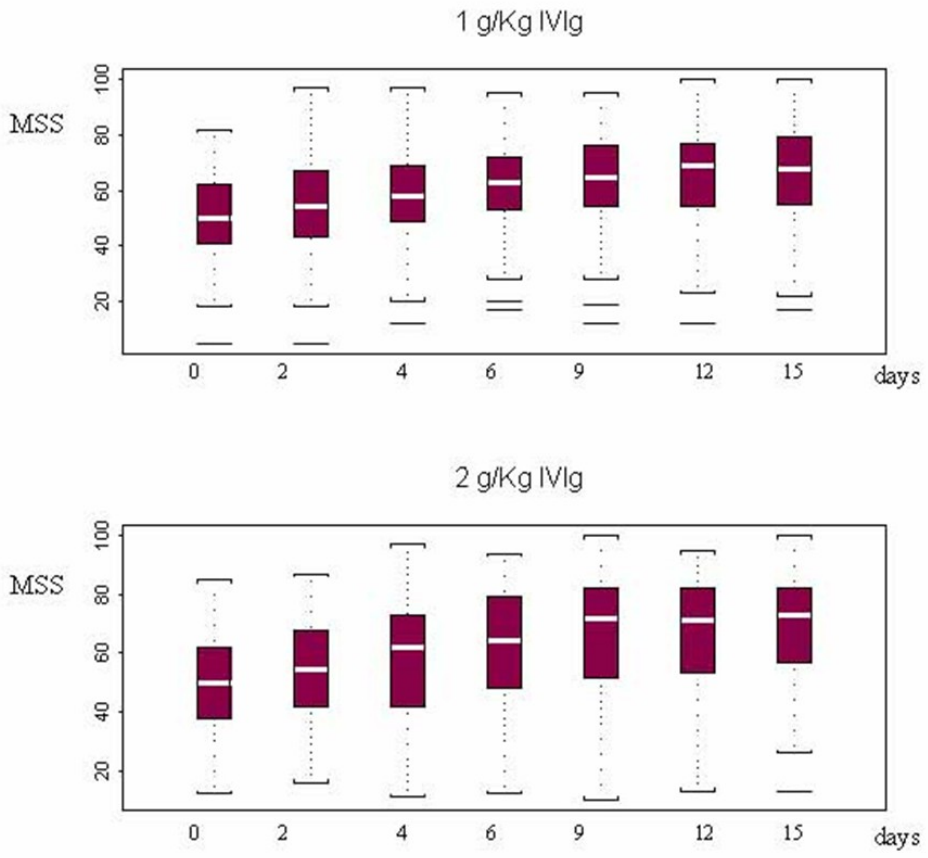
Effets secondaires EP > IVIG

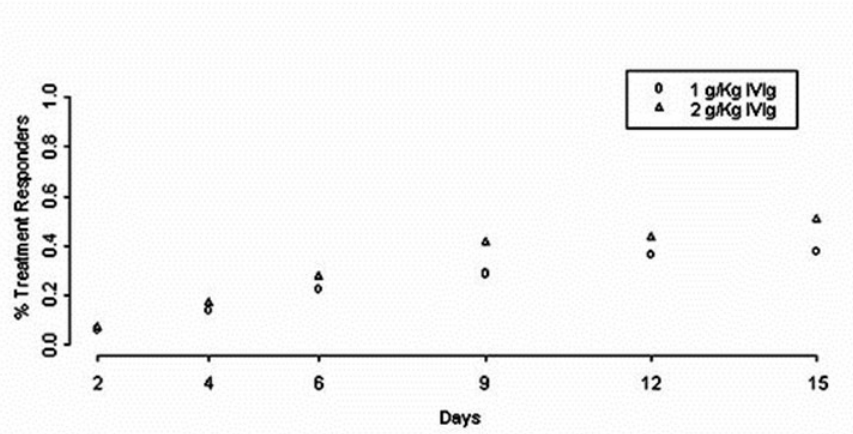
Effets secondaires :	EP	IVIg*
Hémolyse	1	0
Saignements	2	0
Thrombose veineuse KT	1	0
Céphalées	0	1
Fièvre	2	0
HTA	2	0
Frissons	2	0
Nausées, vomissements	1	0
Tachycardie	1	0

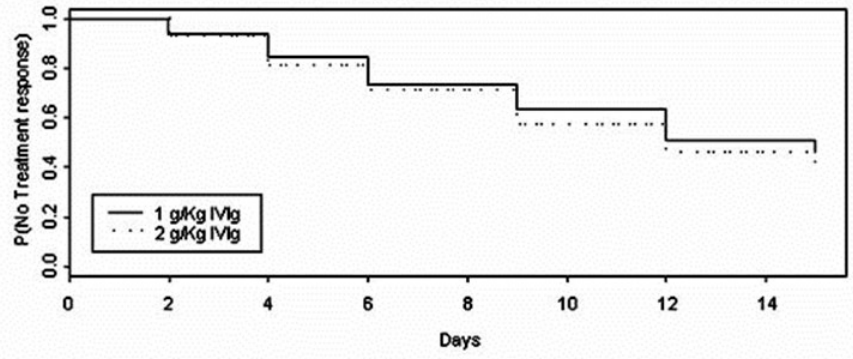
* Dans cette étude, pas d'effets 2aires des IgIV, mais fréquence non négligeable des céphalées et plus rare des réactions allergiques dans d'autres séries

Comparaison de 2 doses IgIV 1g/2g//kg Gajdos et al. 2003

→ Effet identique







Comparaison de 2 doses IgIV 1g/kg versus 2g/kg sur 2 jours
Gajdos et al, 2003
Fréquence effets secondaires légèrement supérieures 2g/kg, mais non significative.

N (%)	1 g/Kg IVIg group **n= 83**	2 g/Kg IVIg group **n= 88**	p-value
Clinical Adverse Events			
Overall number of adverse events (including grade 4)	75 (4)	105 (5)	
Cumulative incidence of patients with clinical adverse event(s) at day 15 (± SD)	49.40 ± 5.49	44.32 ± 5.30	0.44
Fever	10 (12.05)	14 (15.91)	0.51
Chills	3 (3.61)	5 (5.68)	0.72
Myalgia	1 (1.20)	1 (1.14)	1.00
Headaches	11 (13.25)	23 (26.14)	0.037
Nausea-vomiting	5 (6.02)	7 (7.95)	0.77
Neck stiffness	0	1 (1.14)	1.00
Arterial hypotension	0	1 (1.14)	1.00
Tachycardia (> 100/mn)	0	1 (1.14)	1.00
Skin reactions	1 (1.20)	1 (1.14)	1.00
Others	24 (28.92)	28 (31.82)	0.74
Biological Adverse Events			
Increase in serum creatinin level > 120 µmol/L	7 (8.43)	13 (14.77)	0.21
Increase in serum ALT > 2 x upper limit of normal range	7 (8.43)	6 (6.82)	0.78
Increase in serum AST > 2 x upper limit of normal range	3 (3.61)	4 (4.55)	1.00

Indications des IvIg et des Echanges plasmatiques :

1) Indication classique : la poussée sévère (atteinte sévère respiratoire et/ou bulbaire et/ou déficit sévère des membres) en particulier la crise myasthénique

2) Si myasthénie sévère/invalidante rebelle à un traitement bien conduit (corticoïdes + immunosuppresseurs) → plasmaphérèses ou IgIV au long cours en adjonction du traitement immunosuppresseur de de 2ème et 3éme ligne * tant que celui-ci n'est pas efficace

* Immunosuppresseurs de 2nde et 3éme ligne

Mycophenolate Mofetyl (Cellcept) 2g/j, efficacité très inconstamment

Cyclosporine (Neoral, Sandimmun) : adulte 2.5 mg/kg/j

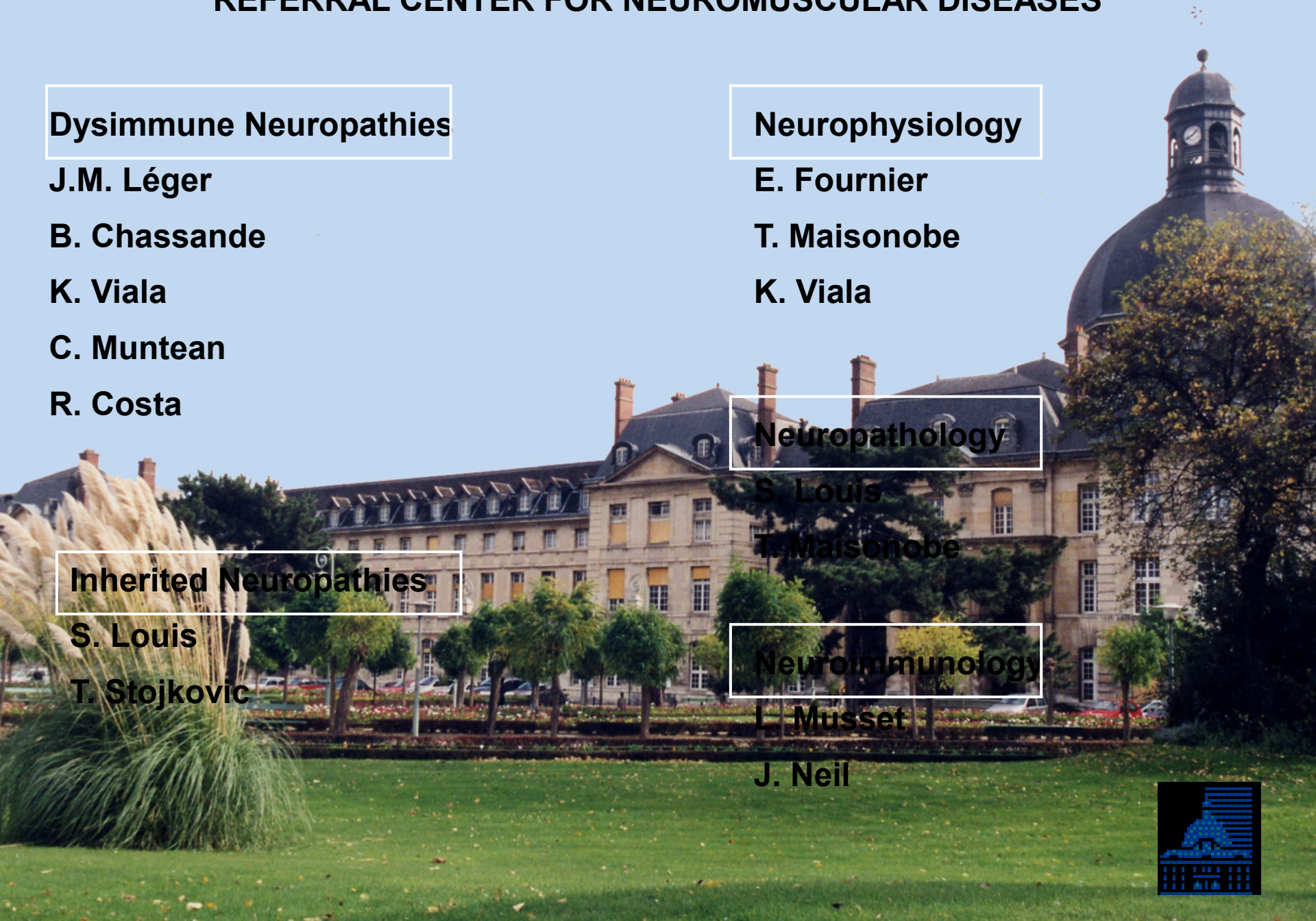
Rituximab (voir infra)

Cyclophosphamide (Endoxan), bolus (voir infra).

Tacrolimus Prograf

3) Indication discutée au cas par cas : préparation à la thymectomie, si contrôle de la myasthénie instable, aggravation au cours de la grossesse.

REFERRAL CENTER FOR NEUROMUSCULAR DISEASES



Dysimmune Neuropathies

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