P7.204

Anti-LINGO-1 Antibody for Treatment of Relapsing Forms of Multiple Sclerosis: Baseline Data of the Phase 2 SYNERGY Trial

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INTRODUCTION

- LINGO-1 (leucine-rich repeat and Ig domain-containing nogo receptor interaction protein-1) is a central nervous system (CNS)-specific membrane glycoprotein that suppresses oligodendrocyte differentiation and myelination and is possibly involved in failure of remyelination and axonal repair in multiple sclerosis (MS).[1]
- Anti-LINGO-1 monoclonal antibody blocks LINGO-1, which may lead to remyelination, neuronal survival, neuronal protection, and axonal regeneration.[1]
- Anti-LINGO-1 was efficacious in preclinical remyelination models and well tolerated in phase 1 human studies.[2]
- The SYNERGY phase 2 trial is assessing the efficacy, safety, tolerability, and pharmacokinetics of anti-LINGO-1 in people with relapsing forms of MS (relapsing-remitting MS [RRMS] and secondary progressive MS [SPMS]) when used concurrently with intramuscular interferon beta-1a (IM IFNβ-1a).

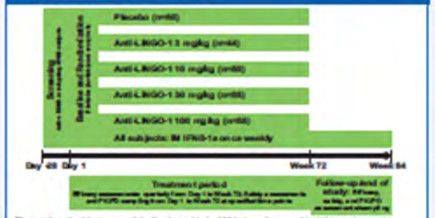
OBJECTIVE

- To present baseline demographic and disease characteristics from the SYNERGY trial of anti-LINGO-1 in participants with active RRMS and relapsing SPMS.

METHODS

- SYNERGY is an ongoing, 84-week, international, multicenter, randomized, double-blind, dose-ranging study evaluating anti-LINGO-1 versus placebo when used concurrently with IM IFNβ-1a in participants with active RRMS/SPMS (NCT01864148).
- Participants receive once-weekly IM IFNβ-1a and are randomized to intravenous infusions of anti-LINGO-1 (3, 10, 30, 100 mg/kg) or placebo once every 4 weeks for 72 weeks (Figure 1).
  - During the follow-up period from weeks 72 to 84, participants continue to receive once-weekly IM IFNβ-1a.

Figure 1. SYNERGY study design



The number of subjects was originally planned to be 396 but was increased to 418 to replace early dropouts due to protocol deviations. IFNβ, interferon beta; IM, intramuscular; IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetic.

- The primary efficacy endpoint is the percentage of subjects with confirmed improvement over 72 weeks of ≥1 component of a composite endpoint comprising neurophysical and/or cognitive function:
  - Expanded Disability Status Scale (EDSS), Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9HPT), and 3-second Paced Auditory Serial Addition Test (PASAT).
- The secondary efficacy endpoint is the percentage of subjects with confirmed worsening of neurophysical and/or cognitive function on the same composite endpoint.
- SYNERGY includes a diverse set of patient-reported outcomes across the spectrum of disability, including walking ability, upper extremity function, general health status, and MS impairments.
- Exploratory endpoints include:
  - Change in cognition as measured using the MS-COG, a composite cognitive endpoint of 2 tests of processing speed (2- and 3- second PASAT and Symbol Digit Modality Test [SDMT]) and 2 tests of memory and learning (Selective Reminding Test [SRT] and Brief Visuospatial Memory Test-Revised [BVMT-R])
  - Severity of clinical relapses measured by Scripps Neurological Rating Scale
  - Worsening from baseline in 6-minute walk (6MW)
  - Analysis of diverse MRI endpoints, including magnetization transfer ratio (MTR) and diffusion tensor imaging (DTI)
- A 2-sample t-test was used to determine baseline differences between RRMS and SPMS subjects.

RESULTS

- Of 633 subjects screened, 418 were randomized and received ≥1 dose of study medication.
- SYNERGY is being conducted at 72 sites in 12 countries, with the majority of participants from Eastern Europe (88%) (Figure 2).
- A total of 330 subjects had RRMS and 88 had SPMS. Demographics for the overall group and by MS type are shown in Table 1.
  - The mean age of all subjects was 40 years, and those with SPMS were older (mean age = 46 years) than those with RRMS (38 years).
  - The majority of subjects were female and white.

Figure 2. SYNERGY study enrollment by country, n (%)

Table 1. Demographic characteristics of SYNERGY participants at baseline

Characteristic	Overall N=418	RRMS n=330	SPMS n=88
Mean (SD) age, years	39.8 (9.5)	38.0 (9.0)	46.4 (8.2)
Female, n (%)	277 (66)	224 (68)	53 (60)
Race, n (%)			
White	398 (95)	311 (94)	87 (99)
Black	6 (1)	6 (2)	0

- MS subjects in SYNERGY demonstrated impairments in physical function and cognitive function at baseline (Table 2).
  - Overall, the mean baseline EDSS score was 3.5, with higher mean scores for those with SPMS (5.2) versus RRMS (3.0).
  - Among all SYNERGY participants, mean T25FW time was prolonged and 6MW distance was shorter compared with normal values; subjects with SPMS showed substantial effects of their disease on walking ability.
  - Baseline 9-HPT results were prolonged for all subjects enrolled in SYNERGY compared to normal values, and results in SPMS subjects were approximately 10 seconds longer than those in RRMS subjects for both hands.
  - At SYNERGY baseline, performance of subjects on the PASAT-2, PASAT-3, SDMT, SRT, and BVMT-R was impaired as compared to normal values, and results for SPMS subjects showed poorer cognitive function versus RRMS subjects.
- Disease characteristics for the overall SYNERGY population are shown in Table 3.
  - Most subjects had 2 or more relapses within the past 2 years (69%).
  - Over half of subjects had taken medication for MS treatment (54%); the most common treatments were IFNβ-1a (19%), glatiramer acetate (18%), IFNβ-1b (9%), natalizumab (7%), and mitoxantrone (6%).
- Baseline MRI characteristics, including diffuse MTR and DTI metrics, are provided in Table 4 for the overall population and by MS type.
  - Subjects with SPMS had higher T1 and T2 lesion volumes and lower brain volumes and Gd+ lesions compared with those with RRMS.

Table 2. Baseline values and comparative normal values for physical and cognitive function[a]

Assessment	Overall N=418	RRMS n=330	SPMS n=88	P Value	Normal Values
EDSS score	3.5 (1.5)	3.0 (1.2)	5.2 (1.0)	<0.0001	
T25FW, seconds				<0.0001	3 – 5[3,4]
Trial 1	7.6 (5.4)	6.4 (3.7)	11.9 (8.1)		
Trial 2	7.5 (5.5)	6.3 (3.7)	11.7 (8.3)		
6MW, meters	398.4 (174.7)	438.5 (165.7)	248.0 (116.3)	<0.0001	571 (90)[5]
9HPT, seconds					16-22[b,3]
Dominant hand				<0.0001	
Trial 1	26.5 (14.5)	23.8 (9.3)	36.7 (23.3)		
Trial 2	25.0 (13.1)	22.4 (8.2)	34.4 (21.3)		
Non-dominant hand				<0.0001	
Trial 1	26.9 (11.7)	24.8 (9.5)	34.6 (15.5)		
Trial 2	25.9 (11.5)	24.0 (10.0)	33.3 (14.0)		
PASAT-3, no. of items	46.1 (12.3)	47.0 (11.8)	42.8 (13.5)	0.0045	49.7 (9.8)[7]
PASAT-2, no. of items	34.3 (11.9)	35.0 (11.4)	31.6 (13.5)	0.0344	37.6 (9.5)[7]
SDMT scores	49.4 (14.6)	51.5 (14.2)	41.6 (13.3)	<0.0001	62.1 (10.7)[7]
SRT, no. of correct answers					
Sum of trials 1-6	48.8 (10.6)	49.9 (10.3)	44.6 (10.6)	<0.0001	Learning: 51.5 (7.3)[7]
Delay trial	7.4 (2.8)	7.7 (2.8)	6.4 (2.7)	0.0002	Recall: 8.4 (2.1)[7]
BVMT-R					
Sum of trials 1-3	23.4 (8.2)	24.1 (8.0)	21.0 (8.6)	0.0017	26.2 (5.8)[7]
Delayed recall	9.0 (3.1)	9.2 (2.9)	8.1 (3.5)	0.0069	10.1 (1.7)[7]

[a]Values are mean (SD) unless otherwise specified; [b]Range for dominant and non-dominant hand for subjects aged 21-60 years. EDSS, Expanded Disability Status Scale; T25FW, timed 25-foot walk; 6MW, 6-minute walk; 9HPT, 9-hole peg test; PASAT, paced auditory serial addition test; SDMT, symbol digit modality test; SRT, selective reminding test; BVMT-R, brief visuospatial memory test-revised.

Table 3. Clinical characteristics of SYNERGY participants at baseline

Characteristic	N=418
Right dominant hand, n (%)	392 (94)
Mean (SD) time since onset of MS symptoms, years	10.1 (8.5)
Mean (SD) time since RRMS diagnosis (n=416), years	6.3 (6.8)
Mean (SD) time since onset of SPMS (n=88), months	40.8 (39.3)
No. of relapses within past 2 years, n (%)	
0	8 (2)
1	122 (29)
2	206 (49)
3	53 (13)
>3	29 (7)
Mean (SD) time since most recent relapse, months	6.9 (7.5)
Subjects who previously took MS medication, n (%)	226 (54)

Table 4. Baseline MRI characteristics[a]

MRI Characteristic	Control N=48	Overall N=418	RRMS n=330	SPMS n=88
No. of Gd+ lesions[a]	NA	1.8 (4.4)	2.0 (4.7)	1.1 (3.3)*
Unenhancing T2 lesion volume, mL	NA	11.5 (14.0)	10.1 (13.3)	16.7 (15.5)*
Unenhancing T1 lesion volume, mL	NA	4.2 (6.2)	3.3 (5.3)	7.4 (8.3)*
Normalized whole brain volume, mL	1495.4(73.7)	1419.5 (88.0)	1433.1 (87.9)	1368.5 (67.9)*
Cortical grey matter volume, mL	573.3(44)	533.3 (49.3)	540.5 (49.3)	506.2 (38.7)*
Thalamic volume, mL	17.2(1.3)	15.1 (2.0)	15.4 (2.0)	14.0 (2.0)*
Median MTR – whole brain[a]	0.31(0.16)	0.21 (0.24)	0.21 (0.25)	0.23 (0.22)*
Median MTR – normal appearing white matter[a]	0.93(0.05)	0.77 (0.22)	0.77 (0.22)	0.76 (0.19)*
Whole brain fractional anisotrophy	0.71(0.03)	0.28 (0.03)	0.28 (0.03)	0.28 (0.03)*
Whole brain radial diffusivity (mm²/s x 10⁻³)	0.71(0.04)	0.74 (0.05)	0.73 (0.04)	0.74 (0.05)*

[a]Values are mean (SD) unless otherwise specified. [b]Median (normalized) MTR: [-2 sMTRu; 2.5 sMTRu]. MTR from a healthy adult subject at each site was used to normalize the MTR values for all MS patients at the site. *P<0.05 for difference between RRMS and SPMS subjects. *P<0.0001 for difference between RRMS and SPMS subjects.

CONCLUSIONS

- The efficacy, safety, and pharmacokinetics of anti-LINGO-1 in participants with active RRMS or relapsing SPMS are being investigated in SYNERGY, a randomized, placebo-controlled, multicenter, phase 2 trial.
- A total of 418 subjects were randomized and dosed in SYNERGY.
- Baseline characteristics in SYNERGY define a population with ongoing relapsing activity and greater pre-existing disability than standard MS trials of disease-modifying treatment.
  - Subjects with SPMS had poorer physical and cognitive function and MRI measures at baseline compared with subjects with RRMS.
- Treatment effects on the various clinical, functional, and MRI measures of efficacy with anti-LINGO-1 over placebo will inform, together with the results of the RENEW study, on its potential value as the first reparative MS therapy.
  - RENEW is the first clinical trial reporting the clinical efficacy and safety of anti-LINGO-1. Further information on the trial and the efficacy and safety results are provided in posters P7.202, P7.203, and P7.206.
- Together the results from the RENEW and SYNERGY studies will inform on the future clinical development of anti-LINGO-1 beyond phase 2.

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Disclosures

DC, SF, YZ, LX: Employees of Biogen; [illegible]

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For an electronic version of this poster, please scan code.

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PLOS | ONE

Azathioprine versus Beta Interferons for Relapsing-Remitting Multiple Sclerosis: A Multicentre Randomized Non-Inferiority Trial

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Abstract

For almost three decades in many countries azathioprine has been used to treat relapsing-remitting multiple sclerosis. However its efficacy was usually considered marginal and following approval of β interferons for this indication it was no longer recommended as first line treatment, even if presently no conclusive direct β interferon-azathioprine comparison exists. To compare azathioprine efficacy versus the currently available β interferons in relapsing-remitting multiple sclerosis, a multicenter, randomized, controlled, single-blinded, non-inferiority trial was conducted in 30 Italian multiple sclerosis centers. Eligible patients (relapsing-remitting course; ≥2 relapses in the last 2 years) were randomly assigned to azathioprine or β interferons. The primary outcome was annualized relapse rate ratio (RR) over 2 years. Key secondary outcome was number of new brain MRI lesions. Patients (n = 150) were randomized in 2 groups (77 azathioprine, 73 β interferons). At 2 years, clinical evaluation was completed in 127 patients (62 azathioprine, 65 β interferons). Annualized relapse rate was 0.26 (95% Confidence Interval, CI, 0.19–0.37) in the azathioprine and 0.39 (95% CI 0.30–0.51) in the interferon group. Non-inferiority analysis showed that azathioprine was at least as effective as β interferons (relapse $RR_{AZA/IFN}$ 0.67, one-sided 95% CI 0.96; $p<0.01$). MRI outcomes were analyzed in 97 patients (50 azathioprine and 47 β interferons). Annualized new T2 lesion rate was 0.76 (95% CI 0.61–0.95) in the azathioprine and 0.69 (95% CI 0.54–0.88) in the interferon group. Treatment discontinuations due to adverse events were higher (20.3% vs. 7.8%, $p = 0.03$) in the azathioprine than in the interferon group, and concentrated within the first months of treatment, whereas in the interferon group discontinuations occurred mainly during the second year. The results of this study indicate that efficacy of azathioprine is not inferior to that of β interferons for patients with relapsing-remitting multiple sclerosis. Considering also the convenience of the oral administration, and the low cost for health service providers, azathioprine may represent an alternative to interferon treatment, while the different side effect profiles of both medications have to be taken into account.

Trial Registration: EudraCT 2006-004937-13

SM e indice UV (esposizione solare)

European Journal of Neurology 2010, **17:** 1210–1214 doi:10.1111/j.1468-1331.2010.03003.x

Genetic and environmental factors and the distribution of multiple sclerosis in Europe

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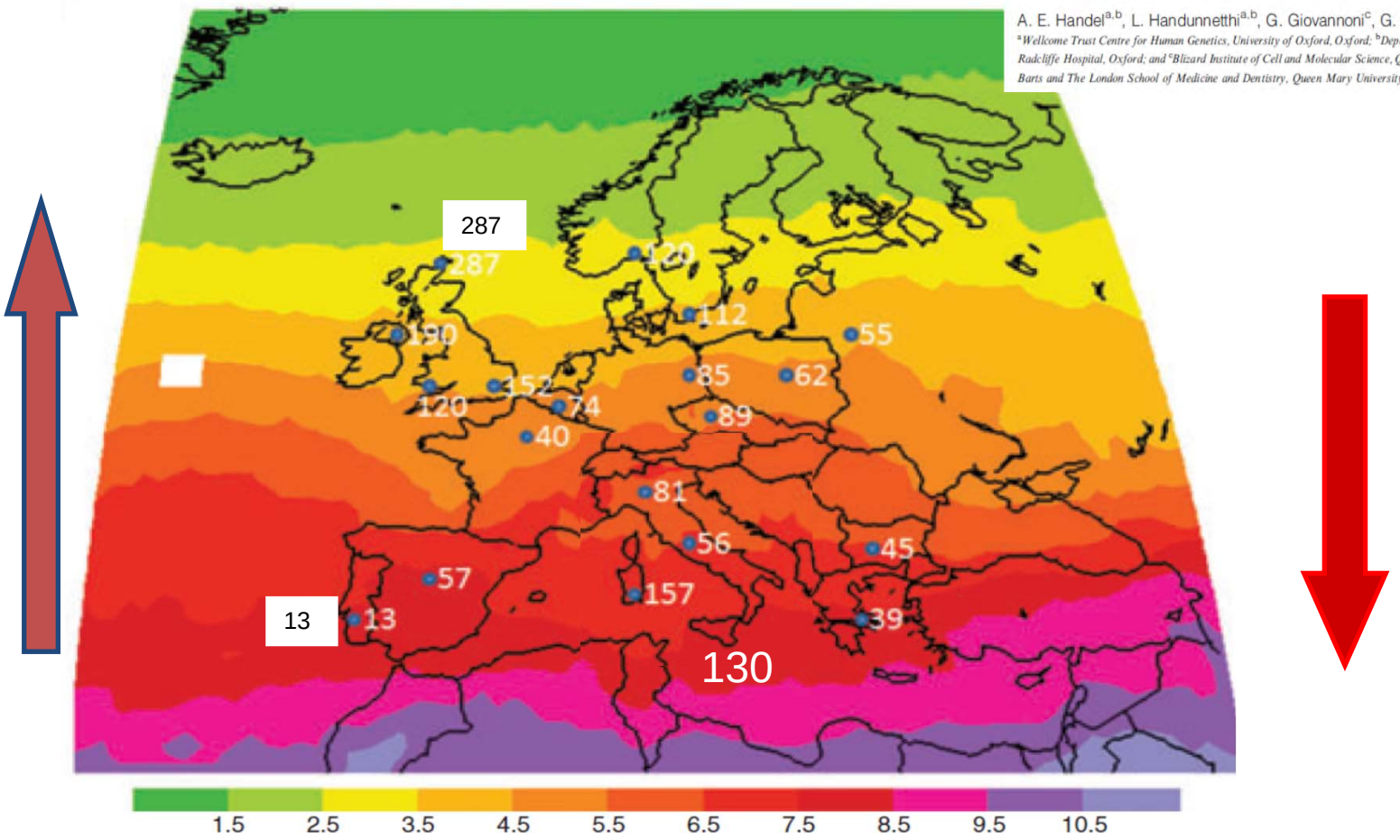
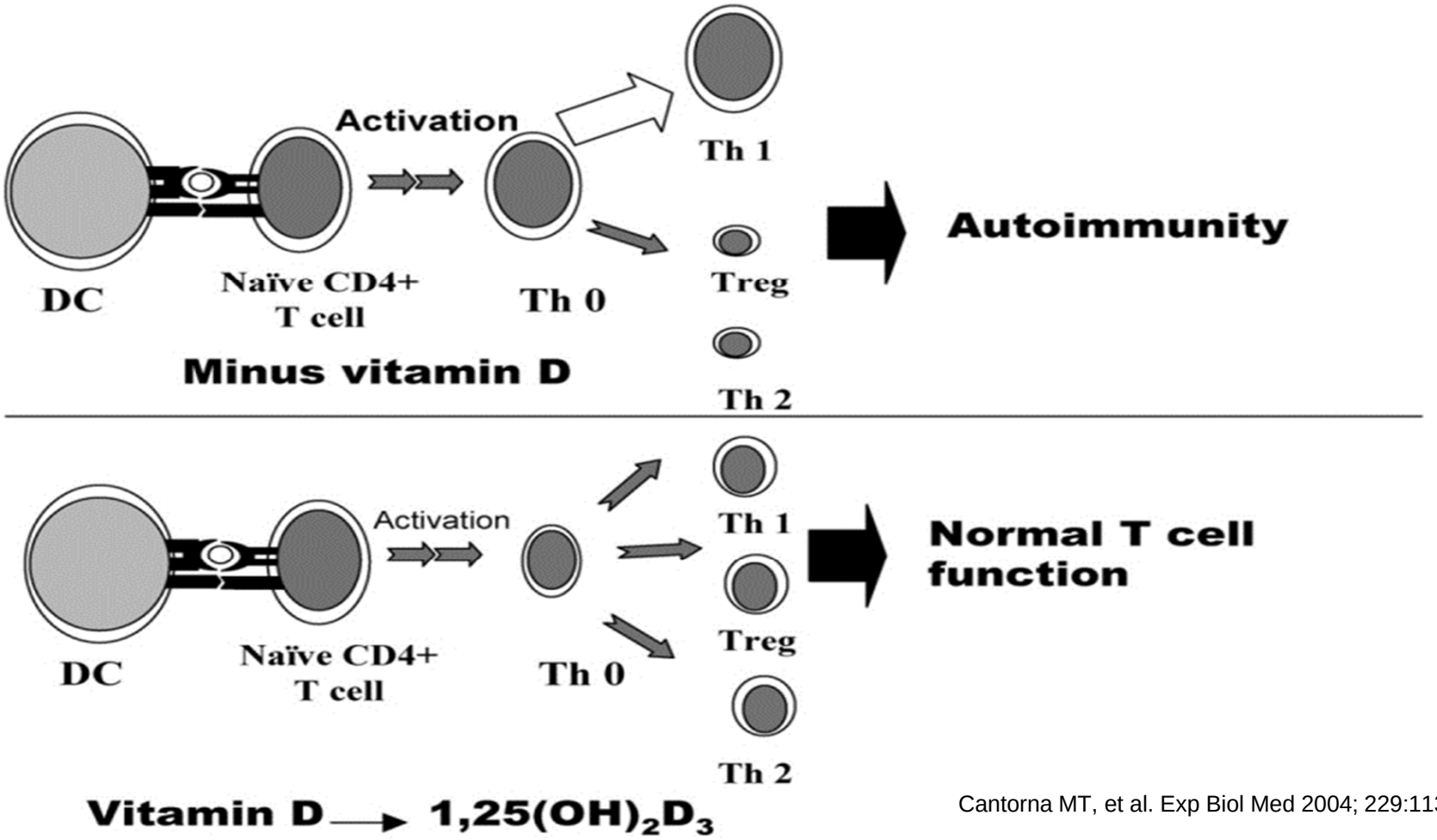


Sclerosi Multipla e ambiente

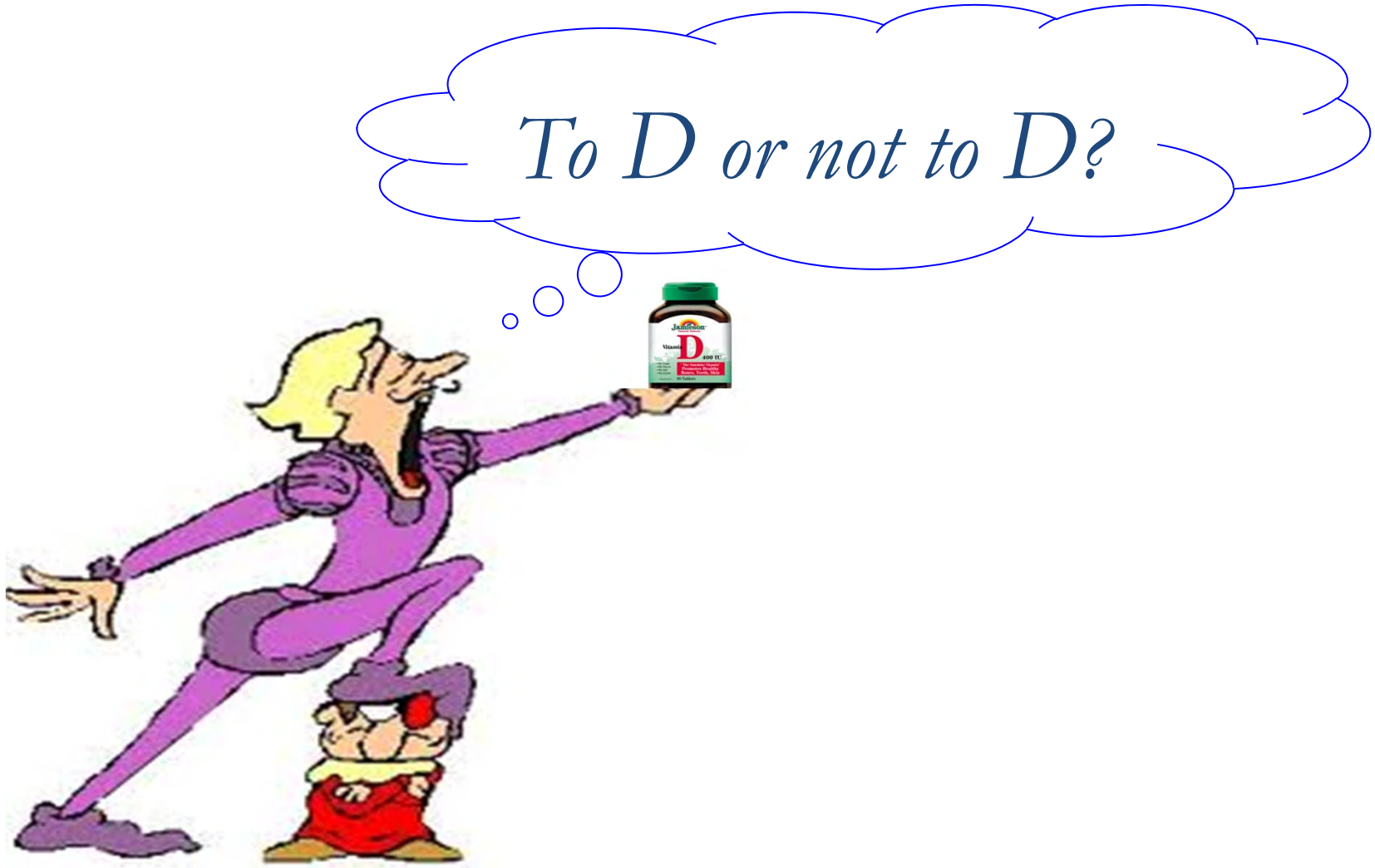
SM e Vitamina D

UV light → higher vitamin D → low MS risk



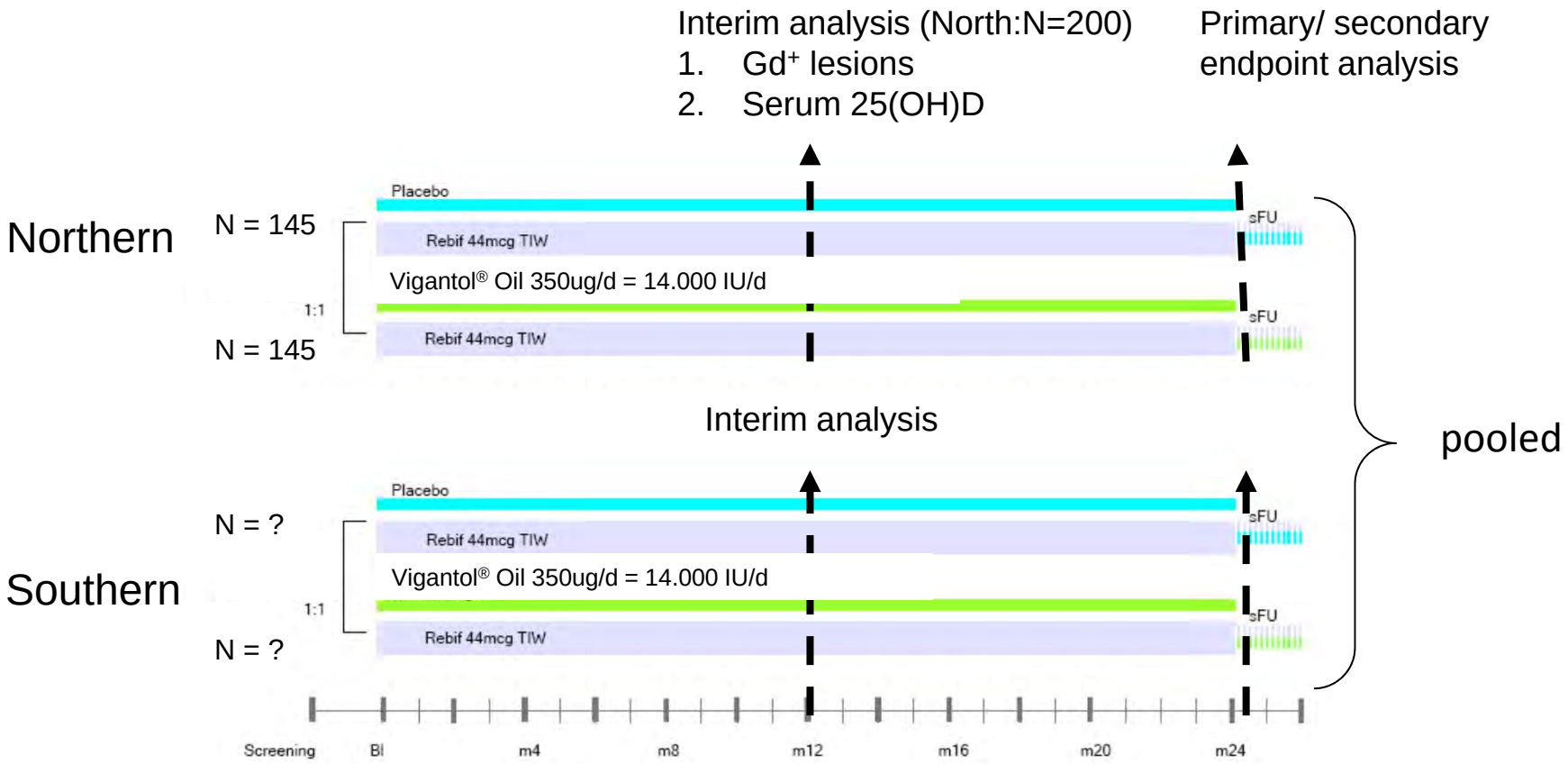
Cantorna MT, et al. Exp Biol Med 2004; 229:1136-42.

SM e Vitamina D: prevenzione?



Sclerosi Multipla e ambiente

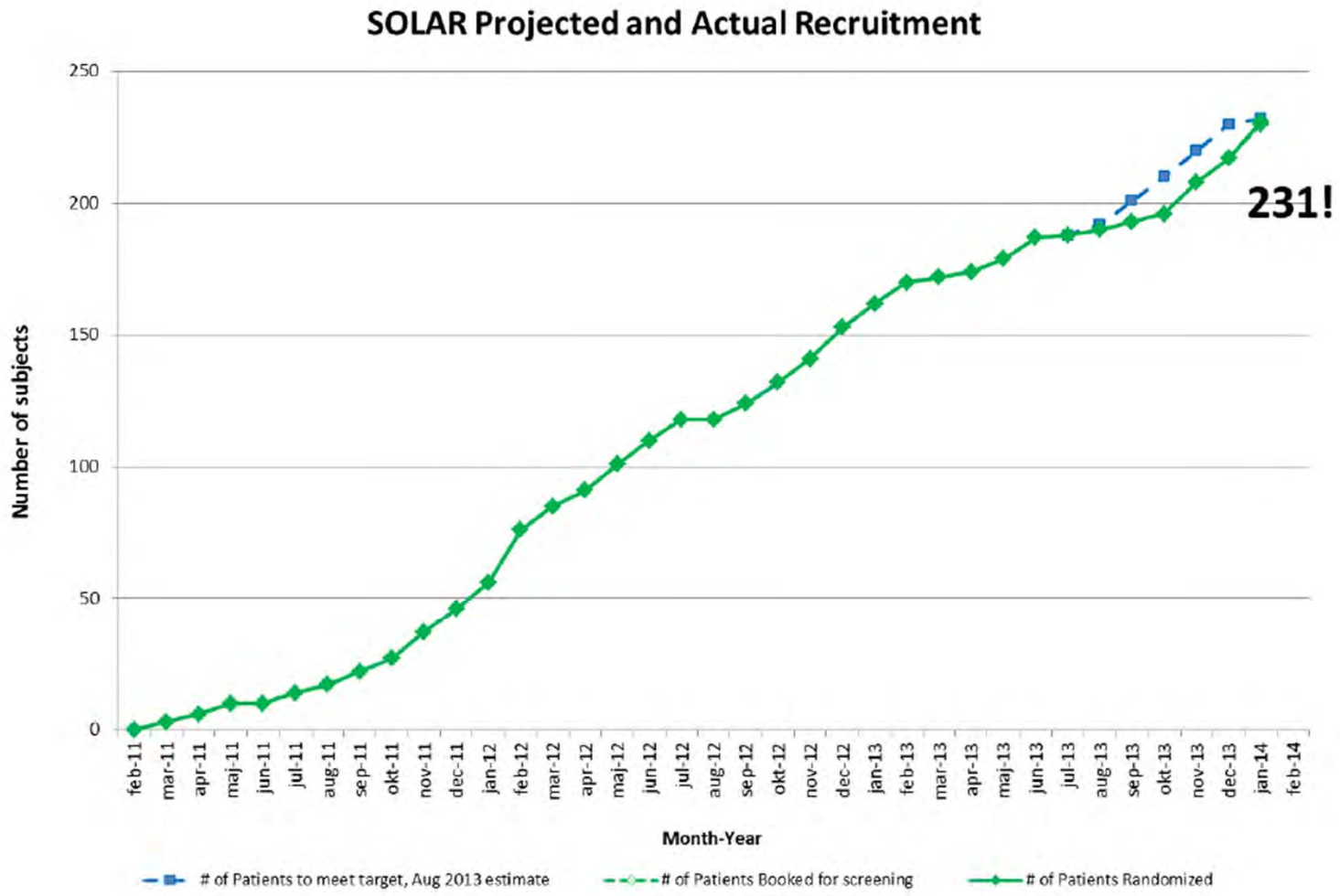
SOLAR: Study Design



At wk 48 interim investigator-blinded analysis for comparability on 25(OH)D and MRI for northern vs. southern countries. If North / South are not different, a pooled analysis can be performed at week 96.

The SOLAR Newsletter

Edition 22, 06th February 2014



SOLAR: enrollment by Center

The current recruitment status (as of 06th February 2014) is:

Country Site	Investigator	Patients Screened	Patients Randomized	Screening failures
Denmark				
101	Dr Frederiksen	12	9	3
102	Dr Sivertsen	3	3	
103	Dr Stenager	5	4	1
104	Dr Stenager	8	8	
105	Dr Stenager	3	2	1
Estonia				
130	Dr Gross-Paju	4	4	
131	Dr Toomsoo	6	6	
Finland				
081	Dr Erälinna	1	1	
082	Prof Färkkilä	3	3	
085	Dr Soilu-Hänninen	6	6	
Germany				
030	Dr De-Hyung Lee	6	6	
031	Dr Dörr	2	2	
032	Prof Griewing	6	6	
033	Prof Kaiser	2	2	
034	Dr Angstwurm	1	1	
036	Dr Marziniak	4	4	
037	Dr Masri	2	1	1
040	Prof Rieckmann	4	2	2
044	Dr Stangel	9	8	1
045	Dr Stich	6	6	
047	Prof Zettl	5	5	

Country Site	Investigator	Patients Screened	Patients Randomized	Screening failures
Italy				
060	Prof Grimaldi	30	30	
Latvia				
110	Dr Kalnina	8	6	1
Lithuania				
121	Dr Mickeviciene	5	3	2
The Netherlands				
001	Dr Frequin	2	2	
003	Prof Hupperts	56	46	10
004	Dr Killestein	5	5	
008	Dr Verheul	5	5	
009	Dr Samijn	8	7	1
Norway				
091	Prof Holmøy	2	2	
092	Prof Myhr	4	4	
093	Dr Kampman	3	2	1
Portugal				
151	Dr Martins da Silva	4	4	
152	Dr Pedrosa	1	1	
153	Dr Salgado	13	10	3
Switzerland				
020	Dr Gobbi	5	4	1
021	Dr Kamm	1	1	
022	Dr Linnebank	2	2	
023	Dr Müller	2	2	
024	Dr Schluep	6	6	
Total		**260**	**231**	**28**

Switching between first-line agents can be beneficial in patients with a suboptimal response

Study	Initial therapy	Therapy switch	Outcome
Caon et al.1	IFN β-1a im	GA	Mean (SD) ARR ↓ from 1.32 to 0.52; p=0.001
Carrá et al.2	IFN β IFN β GA	GA Another IFN β IFN β	ARR ↓ 0.96 to 0.18 ARR ↓ 0.36 to 0.16 ARR ↓ 0.66 to 0.18
Gajofatto et al.3	IFN β GA IFN β	GA IFN β Another IFN β	ARR ↓, but not statistically ARR statistically ↓ ARR statistically ↓
Durelli et al.4	IFN β-1b, 250 mg	IFN β-1b, 375 mg	Proportion of patients without MRI activity during months 9−12 significantly ↓ for IFN β-1b, 375 mg
Rio et al. 5	IFN β IFN β GA	GA Another IFN β IFN β	ARR ↓ 1.1 to 0.25 ARR ↓ 0.9 to 0.27 ARR ↓ 0.82 to 0.16

Adapted from Freedman M *et al.* CMRO 2009;24:2459−70.

[1]Caon C *et al*. Eur J Neurol 2006;13:471–4. [2]Carrá A *et al.* Eur J Neurol 2008;15:386–93. [3]Gajofatto A *et al*. Mult Scler 2009;15:50–8. [4]Durelli L *et al.* J Neurol 2008;255:1315–23. [5]Rio Jet al, Eur J Neurol. 2012; Jun;19(6):899-904

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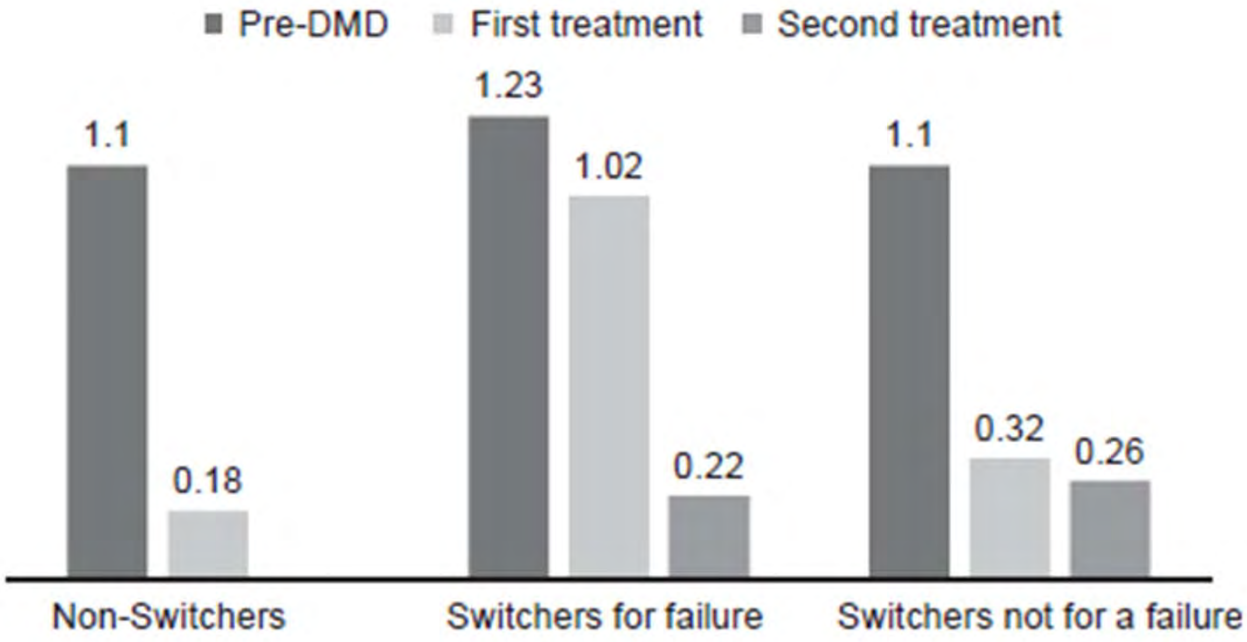
Change in the clinical activity of multiple sclerosis after treatment switch for suboptimal response



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SM: Farmaci di seconda linea

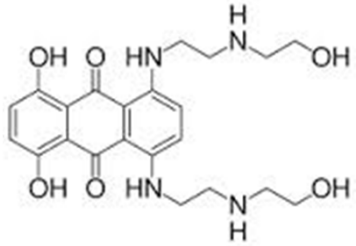
Terapie con diffusa esperienza clinica:
Mitoxantrone, Ciclofosfamide, Natalizumab, Fingolimod

Terapie di recente introduzione:
Alemtuzumab

Terapie in presentazione all'autorità regolatoria:
Cladribina

Terapie in sviluppo:
Rituximab, Ocrelizumab, Ofamumumab, Daclizumab,

Mitoxantrone



Farmaco citotossico derivato dell'antraciclina che esercita la sua azione alterando la struttura del DNA e inibendo l'azione riparativa sul DNA dell'enzima topoisomerasi

Effetto antiproliferativo – riduce:

- Linfociti-B, Linfociti-T, Macrofagi

Effetto immunomodulatorio – riduce:

- La presentazione dell'antigene
- La produzione di citochine (IL-2, Il-10, IFNy, TNFalfa)

Leucemia mieloide acuta dell'adulto (1987)

K prostata avanzato ormono-resistente (1996)

ARTICLES

Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial

Lancet 2002; 360: 2018–25

*Hans-Peter Hartung, Richard Gonsette, Nikolaus König, Hubert Kwiecinski, Andreas Guseo, Sean P Morrissey, Hilmar Kraj Thomas Zwingers, and the Mitoxantrone in Multiple Sclerosis Study Group (MIMS)**

- 188 pz SMSP, worsening SMRR, placebo
- Analisi multivariata di 5 endpoint clinici

(EDSS, Ambulatory Index, tempo alla 1^ ricaduta, n° totale ricadute, Status neurologic

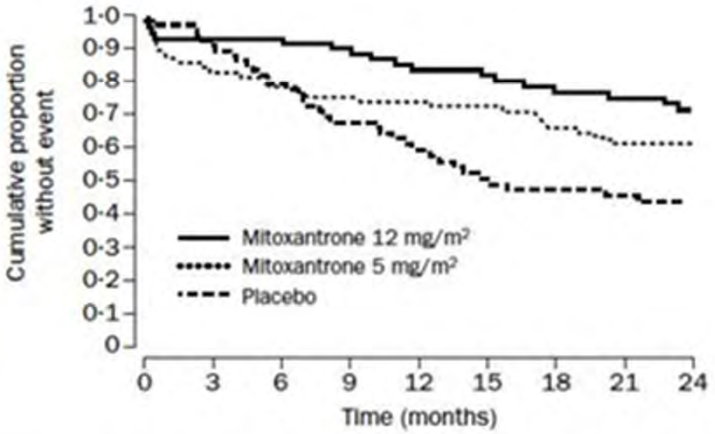


Figure 2: **Time to first treated relapse**

Riduzione progressione disabilità ed esacerbazioni cliniche

Efficacia mantenuta per almeno 12 mesi dopo la sospensione del trattamento

In base allo studio MIMS autorizzazione FDA (2000) per:

- SMRR aggressiva, SMSP, SMPR

Regimi di trattamento:

- 5-12 mg/m^2 ogni 3 mesi (MIMS trial)
- 10 mg/m^2 ogni 4 sett. Per 6 mesi (F-UK trial)

Dose Cumulativa max 140 mg/m^2

Hartung et al., Lancet 2002;Krapf et al., Neurology 2005;Ghalie et al., Neurology 2003; Edan et al., JnnP 1997

Black Box: TRAL

Metanalisi AAN: 0.81% (Marriott JJ et al,*Neurology*, 2010)

0.93%

Neurology. 2011 Nov 22;77(21):1887-95. doi: 10.1212/WNL.0b013e318238ee00. Epub 2011 Nov 9.

Acute myeloid leukemia in Italian patients with multiple sclerosis treated with mitoxantrone.

Martinelli V, Cocco E, Capra R, Salemi G, Gallo P, Capobianco M, Pesci I, Ghezzi A, Pozzilli C, Lugaresi A, Bellantonio P, Amato MP, Grimaldi LM, Trojano M, Mancardi GL, Bergamaschi R, Gasperini C, Rodegher M, Straffi L, Ponzio M, Comi G; Italian Mitoxantrone Group.

0.25%

Mult Scler. 2011 Jul;17(7):867-75. doi: 10.1177/1352458511398371. Epub 2011 Feb 15.

Long-term safety profile of mitoxantrone in a French cohort of 802 multiple sclerosis patients: a 5-year prospective study.

Le Page E, Leray E, Edan G; French Mitoxantrone Safety Group.

0.41%

Incidence of therapy-related acute leukaemia in mitoxantrone-treated multiple sclerosis patients in Germany

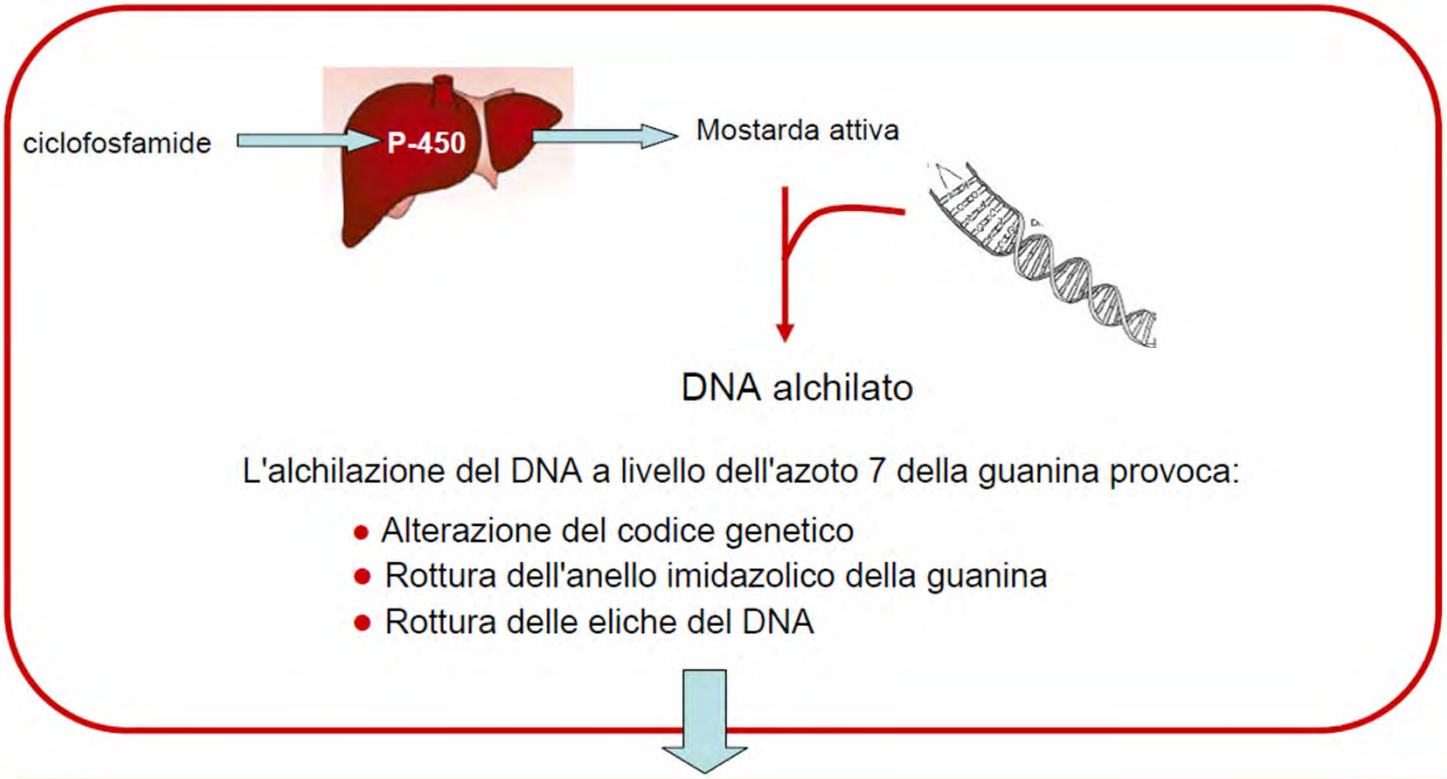
Anke Stroet, Claudia Hemmelmann, Michaela Starck, Uwe Zettl, Jan Dörr, Friedmann Paul, Peter Flachenecker, Vinzenz Fleischer, Frauke Zipp, Holger Nückel, Bernd C Kieseier, Andreas Ziegler, Ralf Gold and Andrew Chan

Ther Adv Neurol Disord
(2012) 5(2) 75–79
DOI: 10.1177/1756285611433318

Ciclofosfamide

La ciclofosfamide è un agente citotossico con potenti effetti immunosoppressori.

Meccanismo d'azione



La ciclofosfamide inibisce la proliferazione cellulare e causa la morte dei linfociti

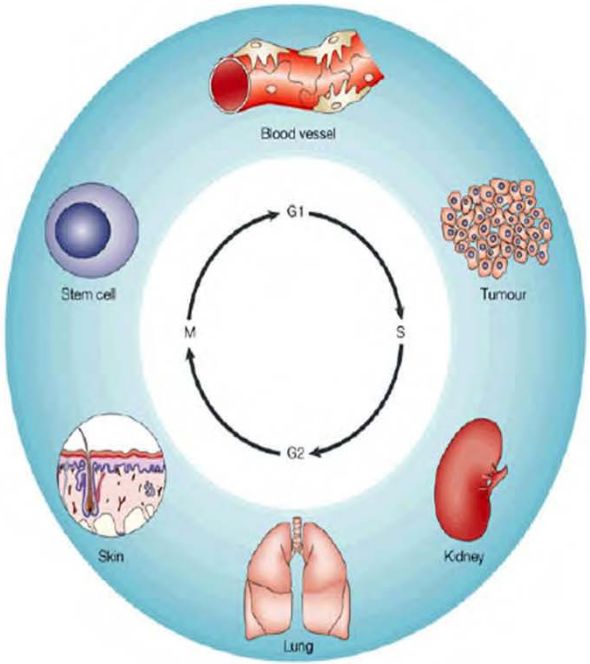
- Riduzione linfociti T helper e linfociti B (meno T supressor)
- Gli effetti sul sistema immunitario persistono per 3-6 mesi dopo sospensione

Cy: safety

EFFETTI COLLATERALI

I principali effetti collaterali della ciclofosfamide sono dovuti alla sua **azione citotossica contro tutti i tessuti proliferanti**

Depressione midollare (leucopenia, trombocitopenia), aumento della suscettibilità alle infezioni, alopecia, sterilità, insorgenza di tumori maligni secondari, nausea, vomito, anoressia



La ciclofosfamide può provocare cistite emorragica (effetto a breve termine) e favorire lo sviluppo di carcinomi secondari prevalentemente localizzati al livello vescicale (effetto a lungo termine)

Potenziali effetti cancerogeni, mutageni e teratogeni. (Rischio fetale)

Regimi terapeutici Cy in SM

AIFA 2011 immunosoppressori con uso consolidato

- Terapia di induzione e.v.: 600 mg/m^2 Cy ai gg 1,2,4,6,8 plus MP per 8 gg
- "Pulse therapy" e.v. con CY/MP: inizio con 800 mg/m^2 e progressivo incremento fino a ottenere leucopenia (3000/mm^3) e linfocitopenia (800/mm^3); ogni 4 settimane per 18-24 mesi, ogni 2 mesi per successivi 24 mesi; Ig MP contestuale.
- "Pulse therapy" con CY a dose fissa: 800-1000 mg/m^2 ogni 4-8 settimane per 12-24 mesi, con o senza MP.
- Terapia di combinazione: Cy e.v. in associazione a IFN beta o GA

HYCY

NIH Public Access
Author Manuscript
Mult Scler. Author manuscript; available in PMC 2013 April 01.

Published in final edited form as:
Mult Scler. 2012 February ; 18(2): 202–209. doi:10.1177/1352458511419701.

Treatment of relapsing–remitting multiple sclerosis with high-dose cyclophosphamide induction followed by glatiramer acetate maintenance

- **200 mg/kg Cy in 4 gg (50 mg/kg/die X 4 gg)**
- **Successivo ciclo di trattamento con filgastrim (fattore di crescita granulocitario)**
- **Inizio di GA dopo 30 gg**

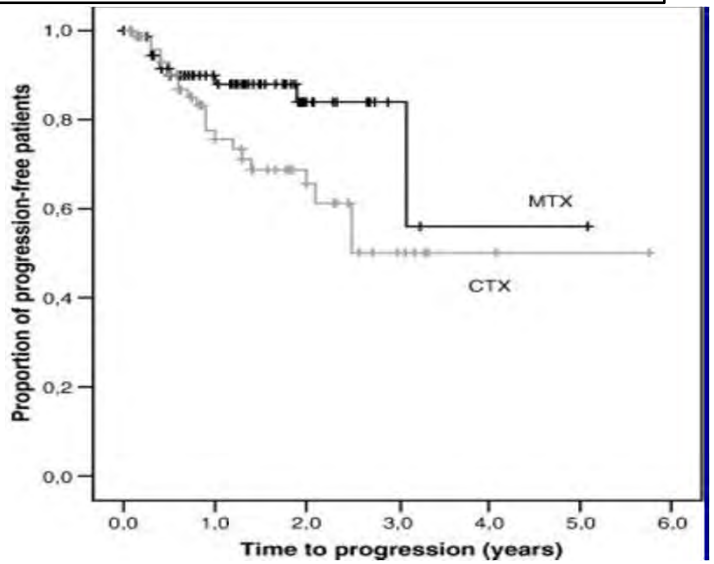
MITOX vs. CY

J Neurol Sci. 2008 Mar 15;266(1-2):25-30. Epub 2007 Sep 17.

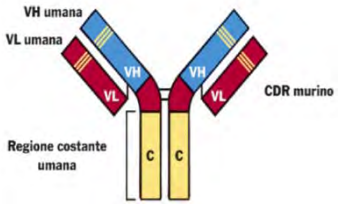
Intravenous mitoxantrone and cyclophosphamide as second-line therapy in multiple sclerosis: an open-label comparative study of efficacy and safety.

Zipoli V, Portaccio E, Hakiki B, Siracusa G, Sorbi S, Amato MP.
Department of Neurology, University of Florence, Viale Morgagni 85, 50134 Florence, Italy.

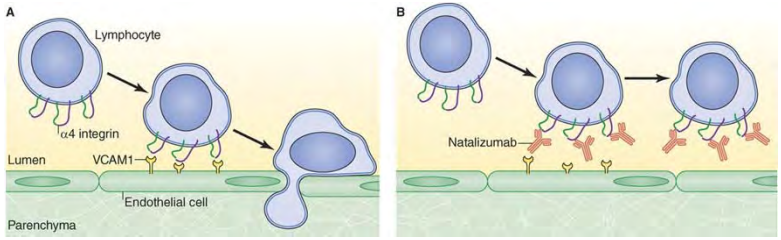
- **RRSM/SPSM con ricadute; FU 3.6 anni**
- **75 Mitox 8 mg/m^2/mese per 3 mesi poi ogni 3 mesi fino DC 120 mg/m^2**
- **Cy 700 mg/m^2/mese per 12 mesi poi ogni 2 mesi per 24 mesi**
- **Non differenze significative tempi 1^ ricaduta (Mitox 2.6, Cy 2.5 aa)**
- **Tempo progressione più breve Mitox (3.8 vs. 3.6 aa)**
- **Riduzione RMN attiva a 12 mesi 69% Mitox e 63% Cy**
- **Drop-out per effetti collaterali più frequente Cy**



Natalizumab



- Anticorpo (IgG4) monoclonale umanizzato anti-integrina leucocitaria umana a4b1 (VLA-4)1



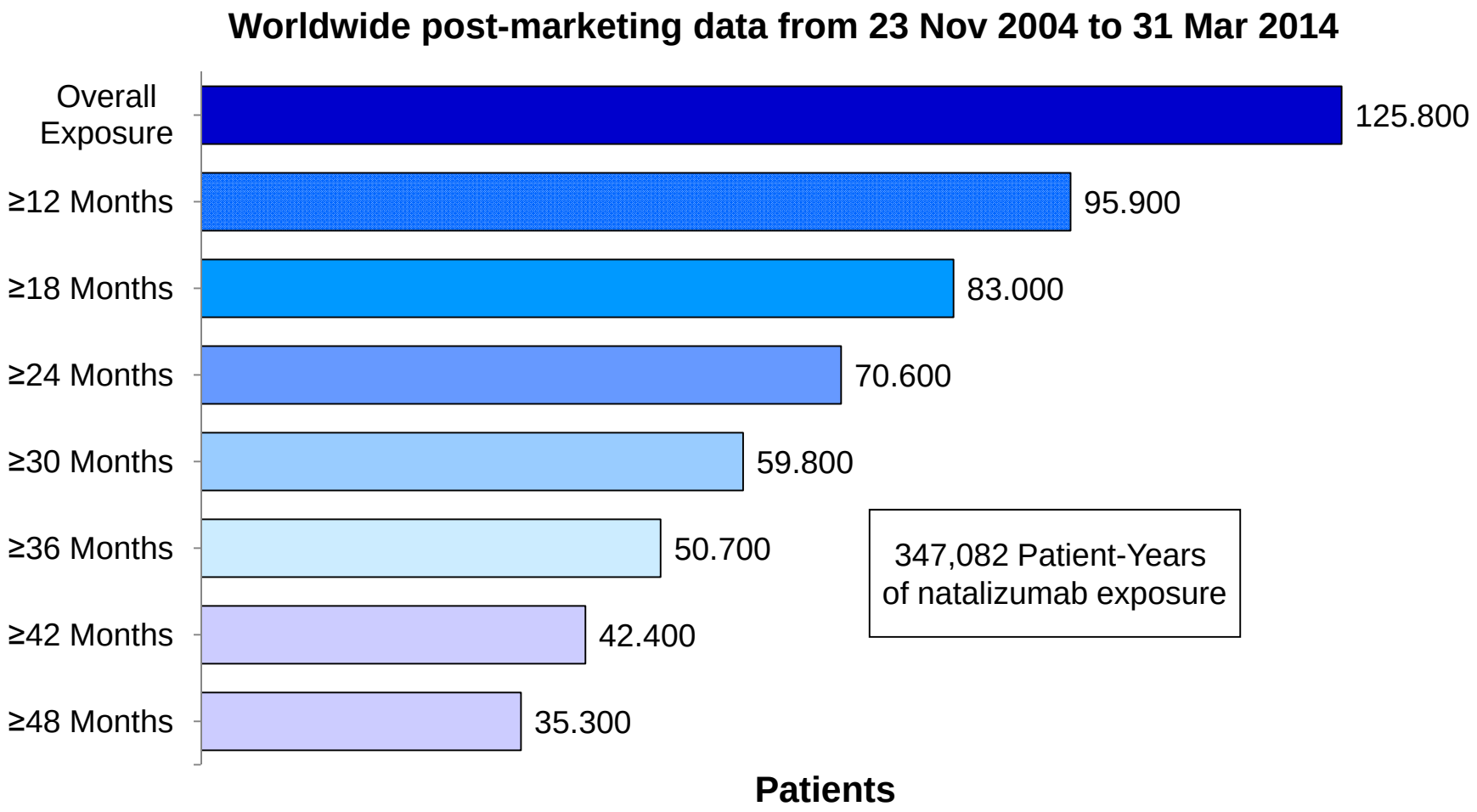
- Impedisce la migrazione transendoteliale dei linfociti Be T e dei monociti nei siti infiammatori
- Lega l'osteopontina, citochina con funzioni pro-infiammatorie e anti-apoptotiche
- Approvato da FDA (2004-2006), EMA ed AIFA (2006) per il trattamento della SMRR in pz che:

- non abbiano risposto a un ciclo terapeutico completo e adeguato con le terapie immunomodulanti attualmente approvate (gruppo A)
- anche non precedentemente trattati con malattia grave a rapida evoluzione (gruppo B)

- Estensione criteri rimborsabilità AIFA (maggio 2011):

- utilizzo precedente GA come farmaco I linea
- utilizzo negli adolescenti di età compresa fra 12 e 18 anni che rientrano nelle caratteristiche gruppo B

Use of Natalizumab in the Post-Marketing Setting*



*Post-marketing data includes patients exposed since 23 November 2004. This excludes approximately 5,100 patients exposed in clinical trials; 2,200 exposed for ≥12 months; 1,900 exposed for ≥18 months; 1,700 exposed for ≥24 months; 1,300 were exposed ≥30 months; 1,000 were exposed ≥36 months; 700 were exposed ≥42 months; and 700 were exposed for ≥48 months. Exposures are estimates and may not fully reflect treatment interruptions that are used in certain patients.

Biogen Idec, data on file.

Natalizumab: gli studi registrativi

Affirm

A Randomized, Placebo-Controlled Trial of Natalizumab for Relapsing Multiple Sclerosis

Chris H. Polman, M.D., Paul W. O'Connor, M.D., Eva Havrdova, M.D., Michael Hutchinson, M.D., Ludwig Kappos, M.D., David H. Miller, M.D., J. Theodore Phillips, M.D., Ph.D., Fred D. Lublin, M.D., Gavin Giovannoni, M.D., Andrzej Wajgt, M.D., Martin Tsal, M.D., M.E.P.M., Frances Lynn, M.Sc., Michael A. Panzara, M.D., M.P.H., ators*

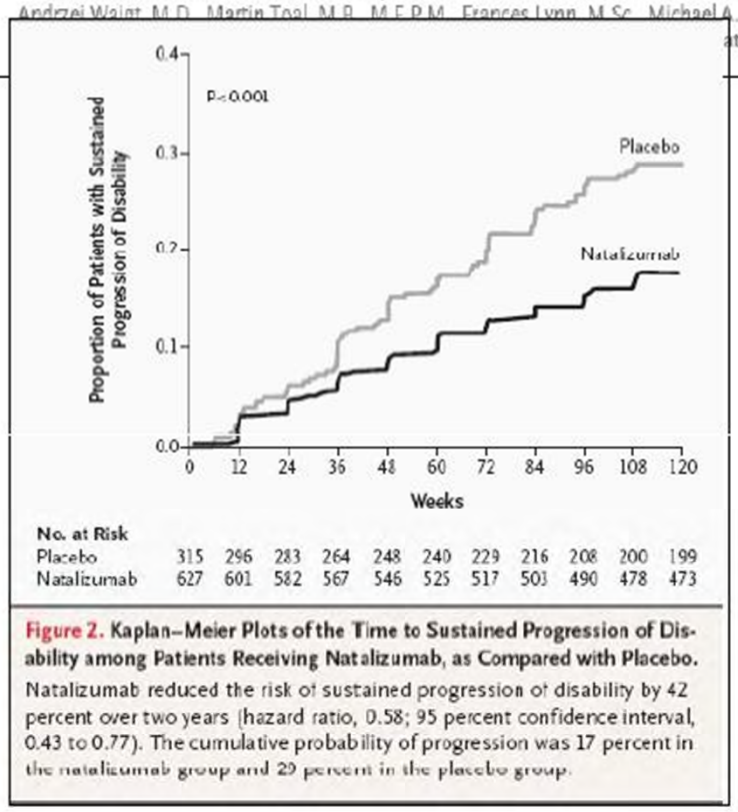


Figure 2. Kaplan–Meier Plots of the Time to Sustained Progression of Disability among Patients Receiving Natalizumab, as Compared with Placebo.
Natalizumab reduced the risk of sustained progression of disability by 42 percent over two years (hazard ratio, 0.58; 95 percent confidence interval, 0.43 to 0.77). The cumulative probability of progression was 17 percent in the natalizumab group and 29 percent in the placebo group.

Sentinel

Natalizumab plus Interferon Beta-1a for Relapsing Multiple Sclerosis

Richard A. Rudick, M.D., William H. Stuart, M.D., Peter A. Calabresi, M.D., Christian Confavreux, M.D., Steven L. Galetta, M.D., Ernst-Wilhelm Radue, M.D., Fred D. Lublin, M.D., Bianca Weinstock-Guttman, M.D., Daniel R. Wynn, M.D., Frances Lynn, M.Sc., Michael A. Panzara, M.D., M.P.H., and Alfred W. Sandrock, M.D., Ph.D., for the SENTINEL Investigators*

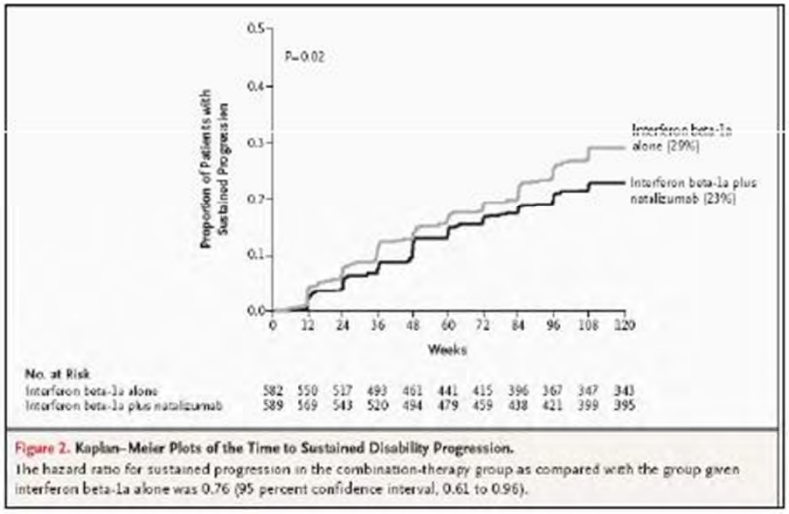


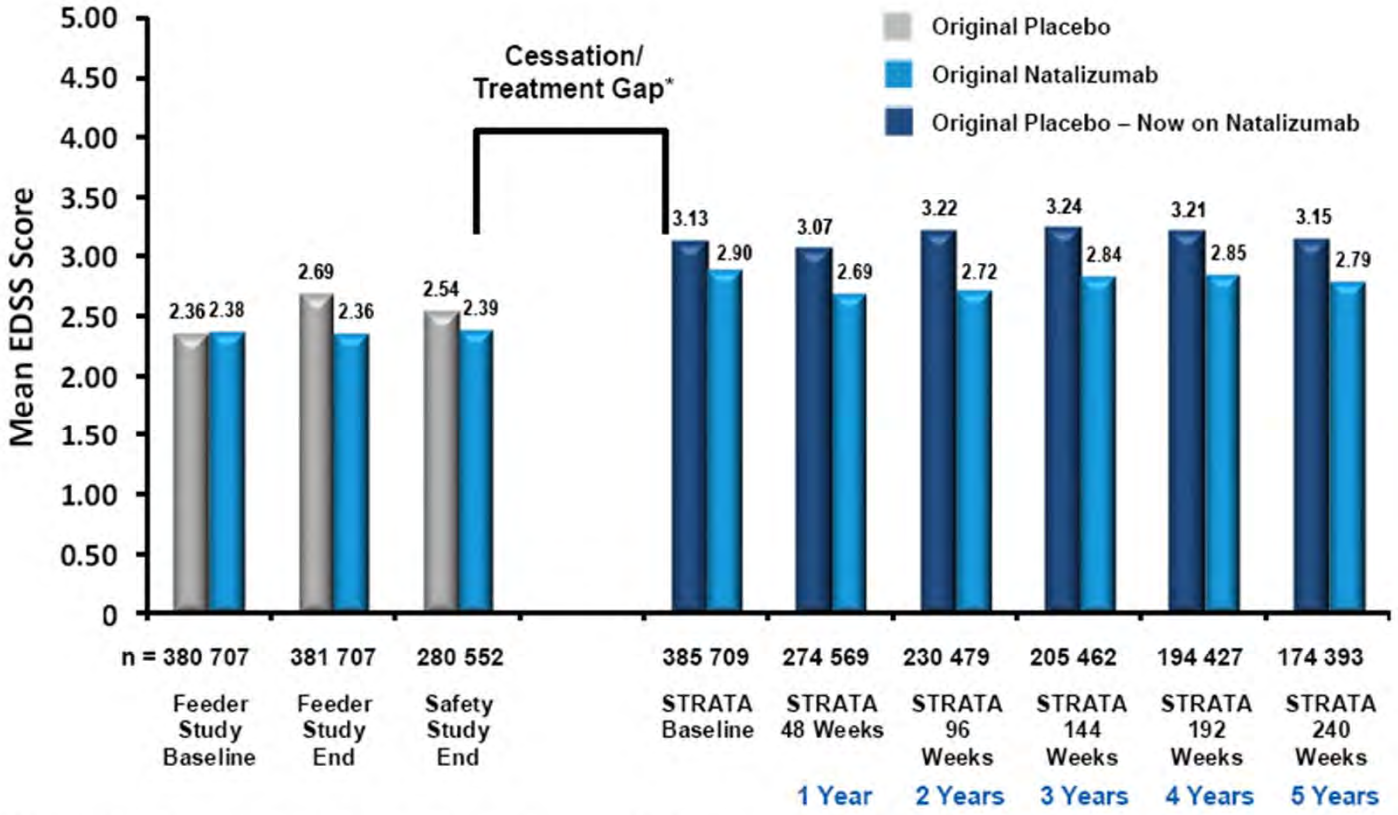
Figure 2. Kaplan–Meier Plots of the Time to Sustained Disability Progression.
The hazard ratio for sustained progression in the combination-therapy group as compared with the group given interferon beta-1a alone was 0.76 (95 percent confidence interval, 0.61 to 0.96).

Clinical Data on Efficacy of Natalizumab: AFFIRM Trial[1]

Endpoint	Net Reduction (vs PBO)	*P*
ARR	−68%	< .001
Mean new or enlarging T2 lesions	−83%	< .001
Mean new GdE lesions	−92%	< .001
Risk of sustained disability progression	−42%	< .001

1. Polman CH et al. *N Engl J Med*. 2006;354:899-810.

STRATA: stabilità EDSS mantenuta a 5 aa



*P<0.0001; †Includes data on patients dosed with natalizumab. EDSS=Expanded Disability Status Scale.
Kappos L et al. Presented at ECTRIMS; October 10–13, 2012; Lyon, France P520.

Predictors of freedom from disease activity in natalizumab treated-patients with multiple sclerosis

Luca Prosperini *, Costanza Giannì, Valeria Barletta, Chiara Mancinelli, Federica Fubelli, Giovanna Borriello, Carlo Pozzilli

Dept. of Neurology and Psychiatry, Multiple Sclerosis Centre, S. Andrea Hospital, Sapienza University, Rome, Italy

ARTICLE INFO

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Keywords:
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Natalizumab
Response to therapy
Freedom from disease activity
Anti-natalizumab antibodies

ABSTRACT

Purpose: To identify baseline predictors of the response to natalizumab in patients with relapsing–remitting multiple sclerosis (RRMS).
Methods: We prospectively collected clinical and magnetic resonance imaging (MRI) data of RRMS patients treated with natalizumab and followed-up for 24 months. They were categorized according to different outcomes of response to natalizumab: (i) "full" responders, i.e. those having no relapses, no sustained disability worsening on Expanded Disability Status Scale (EDSS), and no MRI activity; (ii) "partial" responders, i.e. those having MRI activity, but not relapses and/or EDSS worsening; and (iii) "poor" responder, i.e. those experiencing relapses and/or EDSS worsening.
Results: We analysed data of 210 RR-MS patients (147 F, 63 M); at the end of the 24-month study period, 120 (57.1%), 36 (17.1%), and 54 (25.8%) patients were defined as "full", "partial" or "poor" responders, respectively. Thirty-two (89%) patients classified as "partial" responders experienced MRI activity at the 6-month scan; the majority of them had >2 contrast-enhancing lesions at baseline MRI scan or >2 relapses in the year prior to starting therapy. A "full" response to natalizumab was found more likely in patients with ≤2 relapses in the year prior to treatment start (OR = 3.68; p = 0.002), and in those with an EDSS score ≤2.5 at baseline (OR = 3.60; p < 0.001). Accordingly, patients with >2 relapses in the year prior to treatment start, or those with an EDSS score ≥3.0 at baseline were more likely to be classified as "poor responders". These figures were replicated even after excluding 20 patients who developed anti-natalizumab antibodies.
Conclusion: Our results suggest that natalizumab may lead to a complete remission of MS if started in patients with less aggressive disease (i.e. few relapses and mild disability), thus suggesting its possible role as first switching option, or even first-line therapy, at least in JCV-negative patients. We also support the recommendation against an immediate discontinuation of despite the occurrence of MRI activity in the first few months of treatment, since the freedom from clinical disease activity could be still achieved.

Full responders

- malattia meno aggressiva
- Moderata disabilità

Safety and efficacy of natalizumab in children with multiple sclerosis

A. Ghezzi, MD
C. Pozzilli, MD
L.M.E. Grimaldi, MD
V. Brescia Morra, MD
F. Bortolon, MD
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L. Moiola, MD
M.A. Rocca, MD
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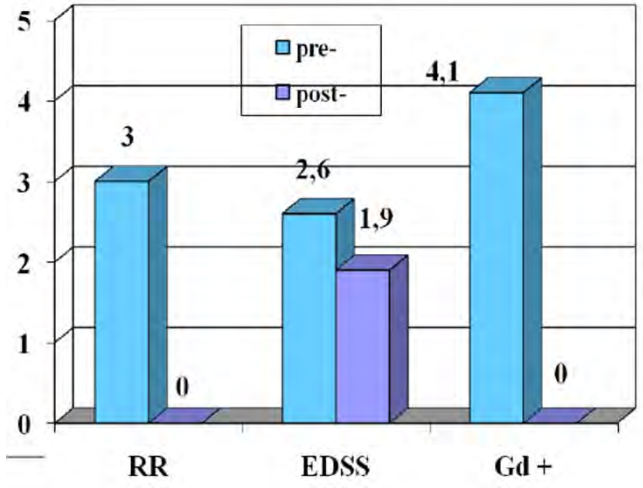
M. Zaffaroni, MD
G. Comi, MD



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ABSTRACT

Objective: To describe the effect of natalizumab in the treatment of subjects with active multiple sclerosis (MS) treated before the age of 18 years.

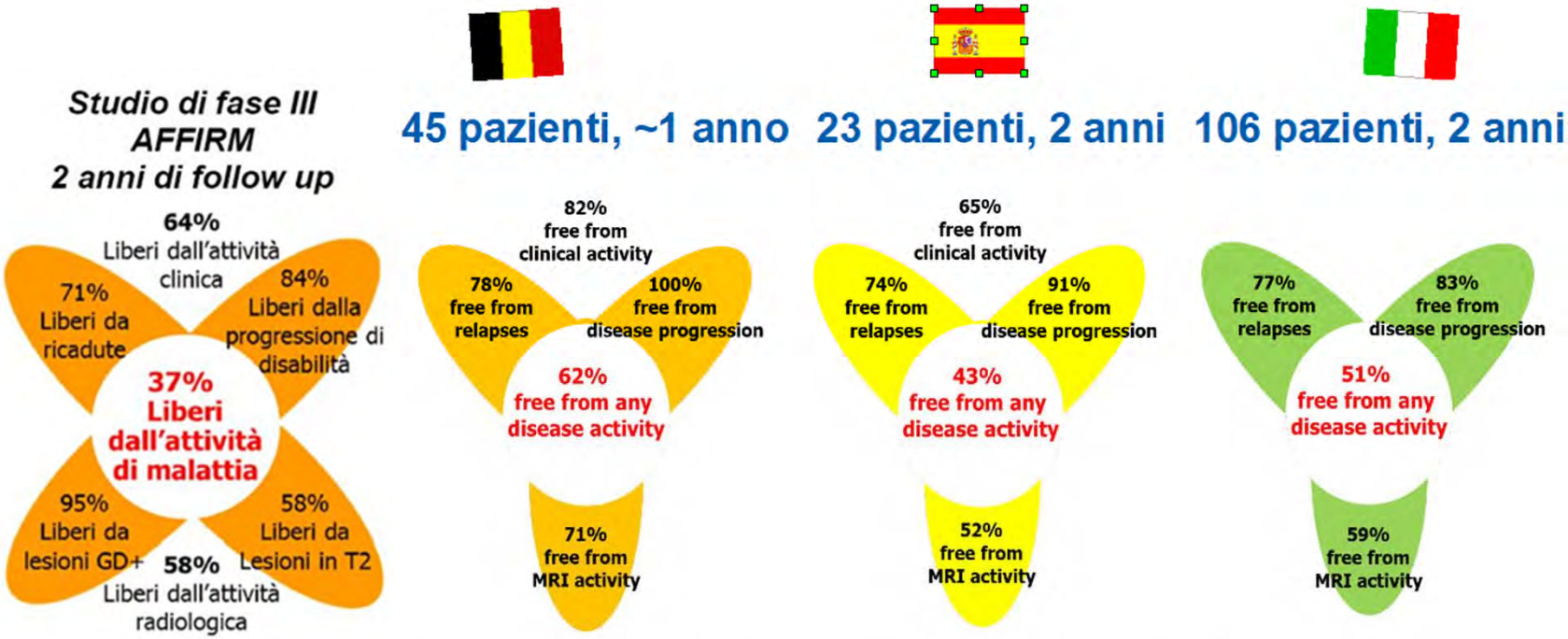
Methods: Nineteen pediatric subjects with MS (mean age 14.6 ± 2.2 years, mean number of attacks 5.2 ± 1.9 during the pretreatment phase of 27.7 ± 19.7 months, median pretreatment Expanded Disability Status Scale score [EDSS] 2.5, range 1.0-5.0) were treated with natalizumab at the dose of 300 mg every 28 days. After treatment initiation, patients were reassessed clinically every month; brain MRI was performed at baseline and every 6 months.

Results: Patients received a median number of 15 infusions (range 6-26). A transient reversible worsening of preexisting symptoms occurred in 1 subject during and following the first infusion. All the patients remained relapse-free during the whole follow-up. The median EDSS decreased from 2.5 to 2.0 at the last visit ($p < 0.001$). EDSS remained stable in 5 cases, decreased by at least 0.5 point in 6 cases, and decreased by at least 1 point in 8 cases. At baseline, the mean number of gadolinium-enhancing lesions was 4.1 (range 1-20). During the follow-up, no gadolinium-enhancing lesions were detected ($p = 0.008$); 3 patients developed new T2-visible lesions at month 6 scan but the overall number of T2 lesions remained stable during the subsequent follow-up. Transient and mild side effects occurred in 8 patients.

Conclusions: Natalizumab was well-tolerated in all subjects. A strong suppression of disease activity was observed in all subjects during the follow-up.

Classification of evidence: This study provides Class IV evidence that natalizumab, 300 mg IV once every 28 days, decreased EDSS scores in pediatric patients with MS over a mean treatment period of 15.2 months. *Neurology*® 2010;75:912-917

Libertà di malattia: AFFIRM e real-life...



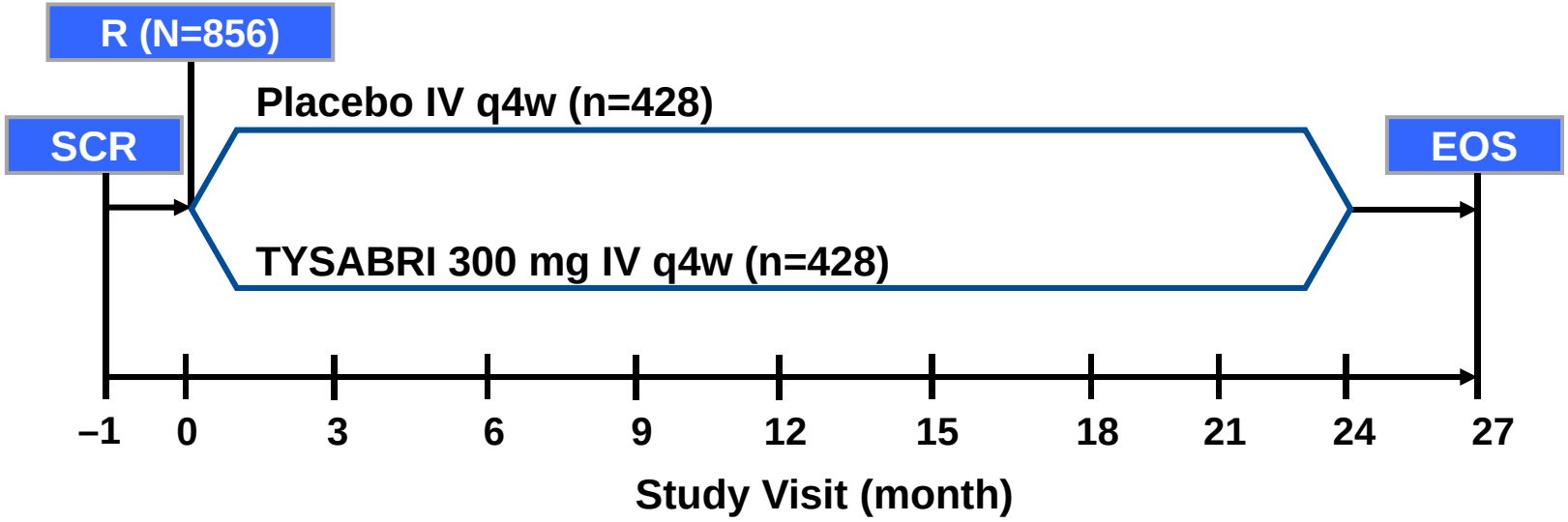
Prosperini L et al. Mult Scler 2012; Melin A et al. J Neurol 2012; Villar LM et al. Arch Neurol 2012.

ASCEND SPMS

A Study to Characterize the Efficacy of Natalizumab on Disability in SPMS

Phase 3 ASCEND SPMS Study Overview

- Study design: phase 3, multicenter, international, randomized, double-blind, placebo-controlled
- Primary endpoint: the percentage of subjects experiencing confirmed progression of disability in one or more of EDSS, T25FW, or 9-HPT
- Key inclusion criteria: SPMS ≥2 years with EDSS 3.0 to 6.5 (inclusive), MSSS ≥4, and evidence of sustained disease progression independent of clinical relapses within prior year; treatment naïve to TYSABRI
- Key exclusion criteria: RRMS, PPMS, relapse ≤3 months, ABCR ≤1 month, immunosuppressants ≤6 months



EDSS=Expanded Disability Status Scale; T25FW=Timed 25-Foot Walk; 9-HPT=9-Hole Peg test; SPMS=secondary progressive MS; MSSS=Multiple Sclerosis Severity Score; PPMS=primary progressive MS; ABCR=AVONEX, Betaseron®, Copaxone®, Rebif®; R=randomized; SCR=screening; q4w=once every 4 weeks; EOS=end of study.
Biogen Idec, data on file.

Natalizumab – Ph 1 PEDIATRIC RRMS

An Entirely Italian Study!

Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis

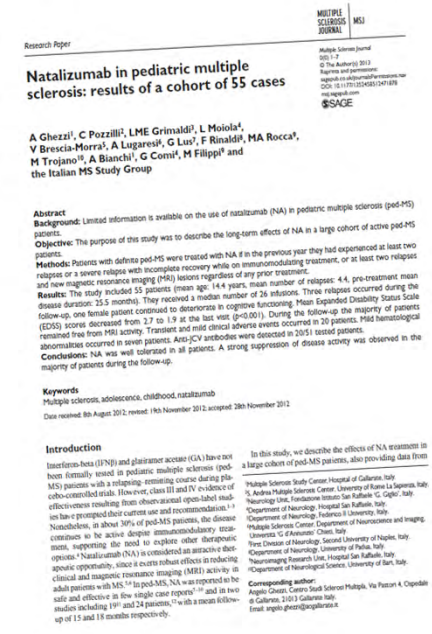
T Chitnis[1], S Tenembaum[2], B Banwell[3], L Krupp[4], D Pohl[5], K Rostasy[6], E A Yeh[7], O Bykova[8], E Wassmer[9], M Tardieu[10], A Kornberg[11], A Ghezzi[12] and for the International Pediatric Multiple Sclerosis Study Group

International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions

Lauren B Krupp[1*], Marc Tardieu[2*], Maria Pia Amato[3], Brenda Banwell[4], Tanuja Chitnis[5], Russell C Dale[6], Angelo Ghezzi[7], Rogier Hintzen[8], Andrew Kornberg[9], Daniela Pohl[10], Kevin Rostasy[11], Silvia Tenembaum[12] and Evangeline Wassmer[13] for the International Pediatric Multiple Sclerosis Study Group

Safety and efficacy of natalizumab in children with multiple sclerosis

A. Ghezzi, MD, C. Pozzilli, MD, L.M.E. Grimaldi, MD, V. Brescia Morra, MD, F. Bernardo, MD, R. Capra, MD, M. Filippi, MD, L. Moiola, MD, M.A. Rocca, MD, M. Rietsch, MD, P. Sacchelli, MD, M. Zaffaroni, MD, G. Comi, MD



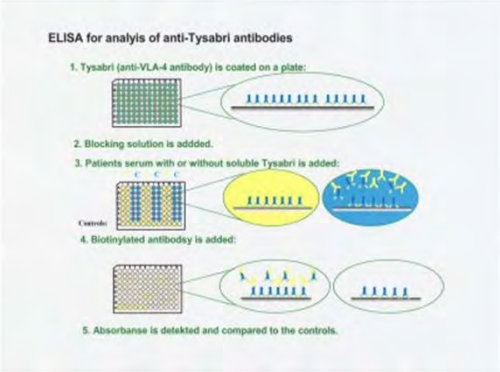
Natalizumab in pediatric multiple sclerosis: results of a cohort of 55 cases

A Ghezzi[1], C Pozzilli[2], LME Grimaldi[3], L Moiola[4], V Brescia-Morra[5], A Lugaresi[6], G Lus[7], F Rinaldi[8], MA Rocca[9], M Trojano[10], A Bianchi[1], G Comi[4], M Filippi[9] and the Italian MS Study Group

Natalizumab

Problemi: i non responders

Nabs



ARTICLES

The incidence and significance of anti-natalizumab antibodies

Results from AFFIRM and SENTINEL

Results: In the AFFIRM study, antibodies were detected in 57 of 625 (9%) of natalizumab-treated patients: Twenty (3%) were transiently positive and 37 (6%) were persistently positive.

In transiently positive patients, full efficacy was achieved after approximately 6 months of treatment, the time when patients were becoming antibody negative. The incidence of infusion-related adverse events was significantly higher in persistently positive patients.

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

Occurrence of antibodies against natalizumab in relapsing multiple sclerosis patients treated with natalizumab

Multiple Sclerosis Journal
0(00) 1–5

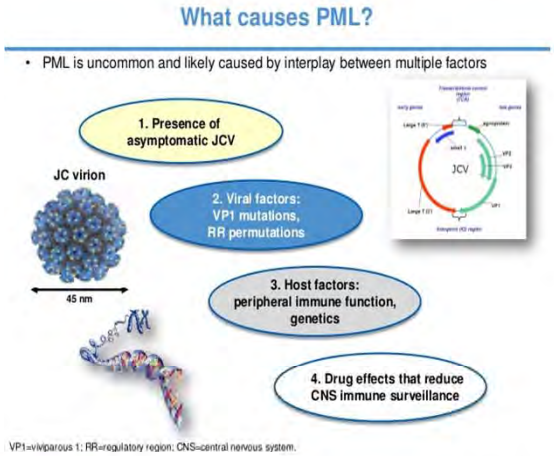
DOI: 10.1177/1352458511404271
msj.sagepub.com
SAGE

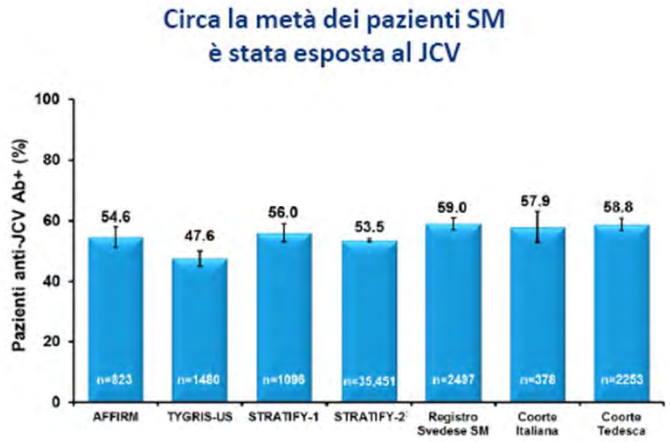
Methods: We measured anti-natalizumab antibodies in a large cohort of 4881 unselected patients from four MS centres that systematically measured antibodies in patients treated with natalizumab. We applied the same ELISA assay developed by Biogen Idec and used in the pivotal trials of natalizumab.

Results: Antibodies occurred in 4.5% (95% confidence interval, CI: 4.0–5.1%) of the patients, and were persistent in 3.5% (95% CI: 3.0–4.0%) and transient in 1.0% (95% CI: 0.7–1.3%) of the patients. The frequencies of permanently

Natalizumab

Problemi: la PML





The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Risk of Natalizumab-Associated Progressive Multifocal Leukoencephalopathy

Gary Bloomgren, M.D., Sandra Richman, M.D., Christophe Hotermans, M.D., Meena Subramanyam, Ph.D., Susan Goelz, Ph.D., Amy Natarajan, M.S., Sophia Lee, Ph.D., Tatiana Plavina, Ph.D., James V. Scanlon, Pharm.D., Alfred Sandrock, M.D., and Carmen Bozic, M.D.

From Biogen Idec, Weston, MA. Address reprint requests to Dr. Bloomgren at Biogen Idec, 14 Cambridge Center, Cambridge, MA 02142, or at gary.bloomgren@biogenidec.com.

N Engl J Med 2012;366:1870-80.

ABSTRACT

BACKGROUND

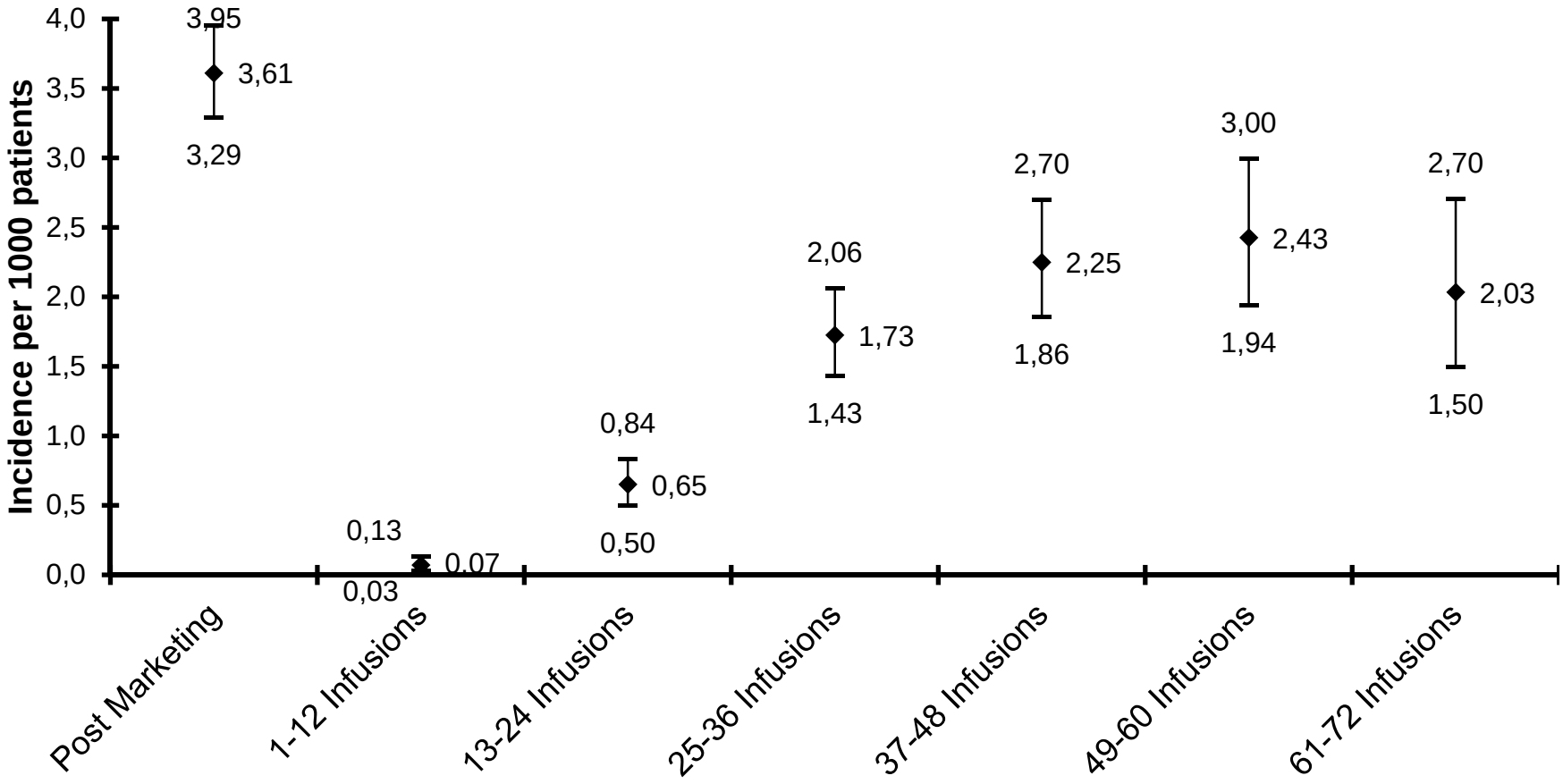
Progressive multifocal leukoencephalopathy (PML) is associated with natalizumab treatment. We quantified the risk of PML in patients with multiple sclerosis, according to the presence or absence of three risk factors: positive status with respect to anti–JC virus antibodies, prior use of immunosuppressants, and increasing duration of natalizumab treatment.

- Rara malattia demielinizzante del SNC potenzialmente mortale e sempre invalidante
- Causata dall'attivazione del virus JC, presente nella maggioranza degli adulti sani in forma latente
- Espressività clinica e neuroradiologica eterogenea

PML

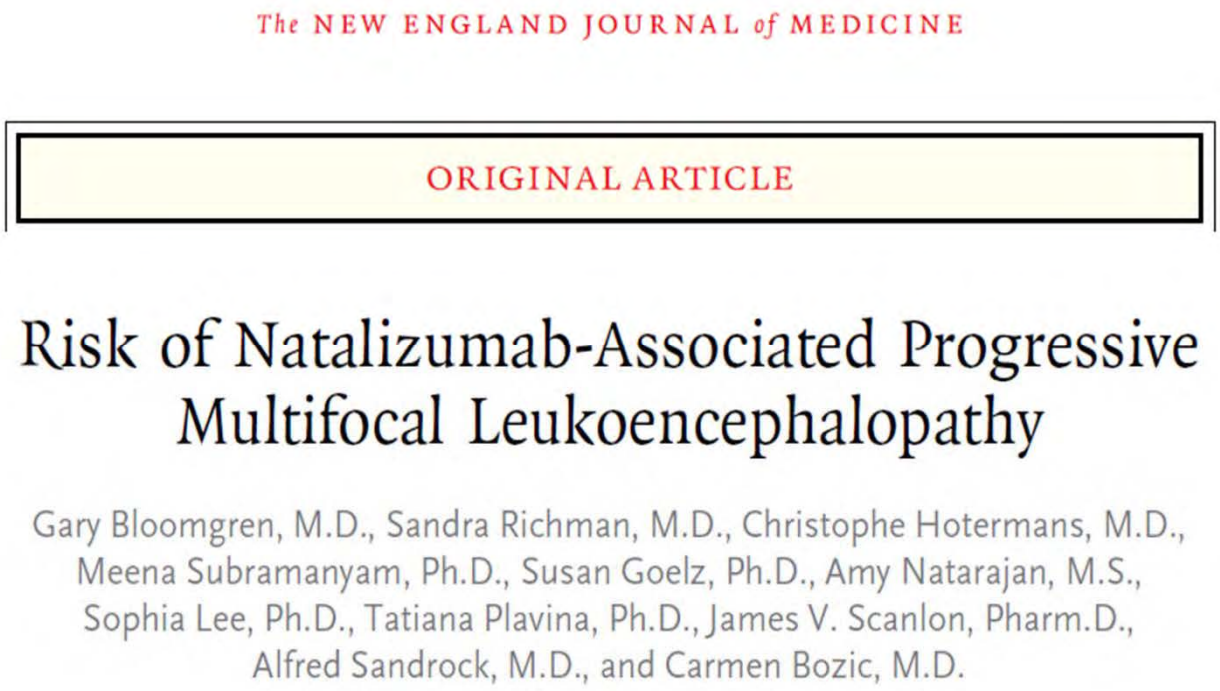
Incidence in Natalizumab-treated Patients by Treatment Epoch*

464 cases, 106 pts died



* **April 14, 2014**

PML risk stratification



The NEW ENGLAND JOURNAL of MEDICINE

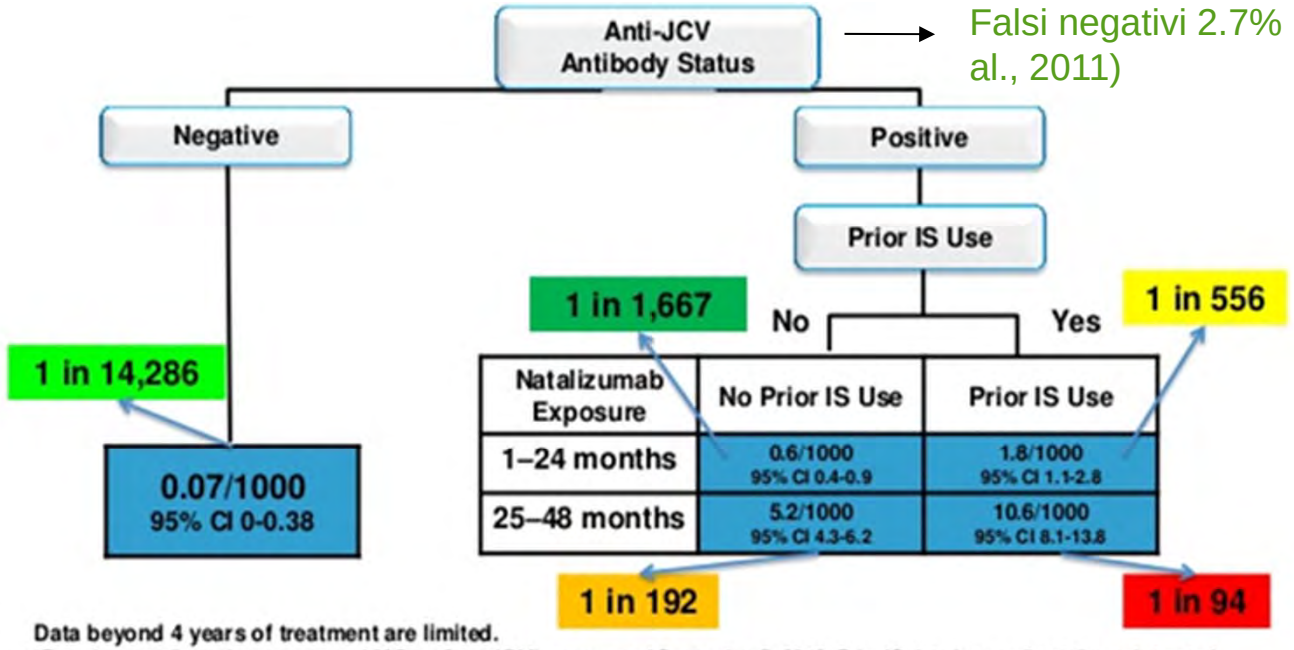
ORIGINAL ARTICLE

Risk of Natalizumab-Associated Progressive Multifocal Leukoencephalopathy

Gary Bloomgren, M.D., Sandra Richman, M.D., Christophe Hotermans, M.D., Meena Subramanyam, Ph.D., Susan Goelz, Ph.D., Amy Natarajan, M.S., Sophia Lee, Ph.D., Tatiana Plavina, Ph.D., James V. Scanlon, Pharm.D., Alfred Sandrock, M.D., and Carmen Bozic, M.D.

- Positive status to anti-JCV antibodies
- Prior use of other immunosuppressive therapy
- Duration of natalizumab treatment

Stratificazione rischio: JCV Ab+, precedente IS, durata trattamento



Data beyond 4 years of treatment are limited.

*Based on natalizumab exposure and 285 confirmed PML cases as of September 5, 2012. Prior IS data in overall natalizumab-treated patients based on proportion of patients with IS use prior to natalizumab therapy in TYGRIS as of May 2011; and prior IS data in PML patients as of September 5, 2012. The analysis assumes that 55% of natalizumab-treated MS patients were anti-JCV antibody positive and that all PML patients test positive for anti-JCV antibodies prior to the onset and diagnosis of PML. The estimate of PML incidence in anti-JCV antibody negative patients is based on the assumption that all patients received at least 1 dose of natalizumab . Assuming that all patients received at least 18 doses of natalizumab , the estimate of PML incidence in anti-JCV antibody negative patients was generally consistent (0.1/1000; 95% CI 0.00–0.62).

Biogen Idec, data on file.

- Assenza associazione tipo e durata trattamento IS
- A breve disponibilità valutazione quantitativa JCV

46 y, esordio aggressivo SM inizio 2008

6 mesi: 3 ricadute

Emisindrome cerebellare sinistra con atassia della marcia, tremore della voce e del capo, dismetria I-N a sin, tremore intenzionale arto sup sin
EDSS: 3.5

RM esordio: numerose lesioni della SB, > 10 captanti

NATALIZUMAB prima linea

Fondazione Istituto San Raffaele G. Giglio di Cefalù

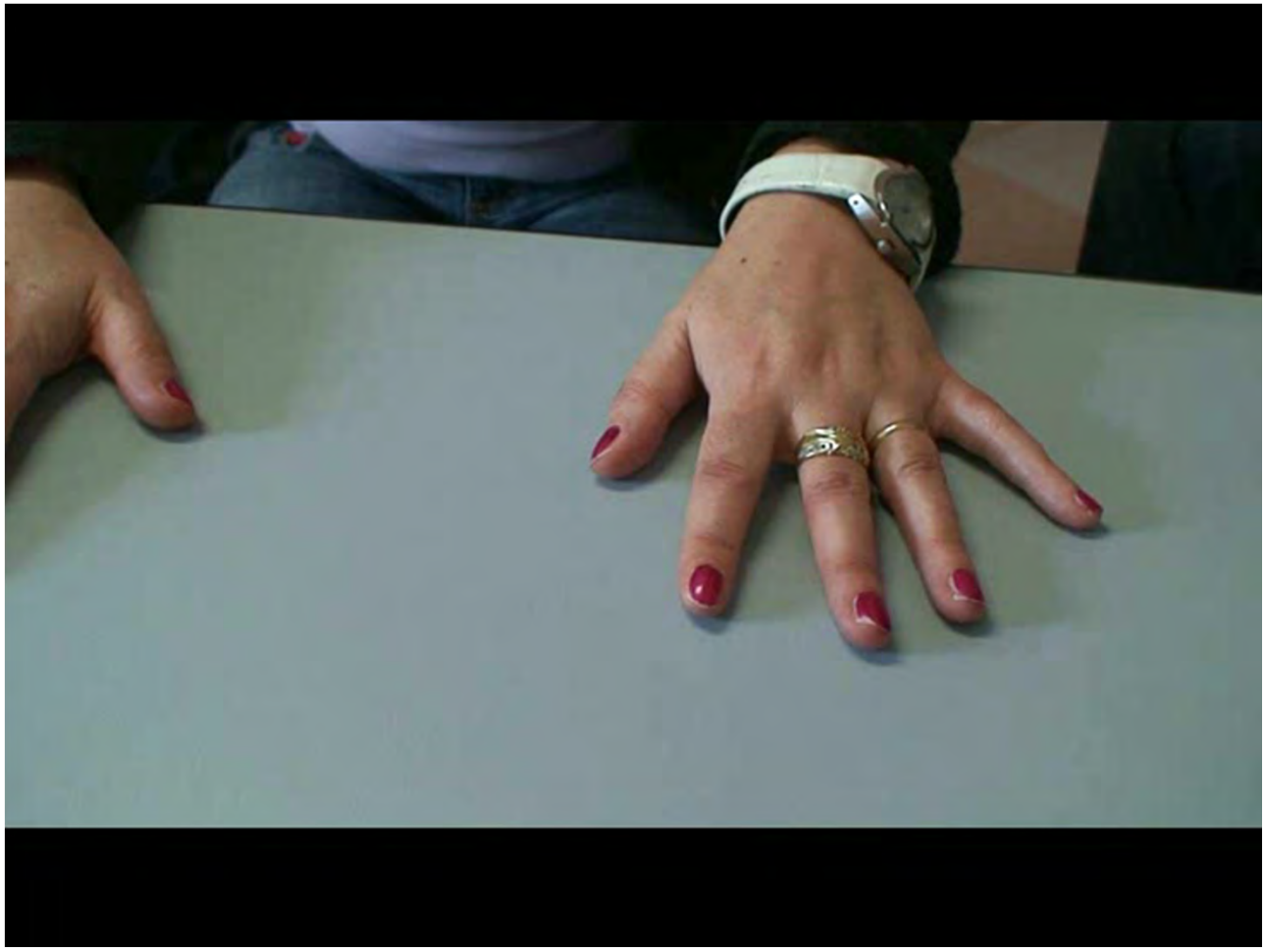
Novembre 2010

- ***Anti-JCV: positiva***
- ***> 24 somministrazioni***
- ***No precedente immunosoppressori***

PROSEGUE TERAPIA CON NATALIZUMAB

Fondazione Istituto San Raffaele G. Giglio di Cefalu

Gennaio 2012: 46° somministrazione



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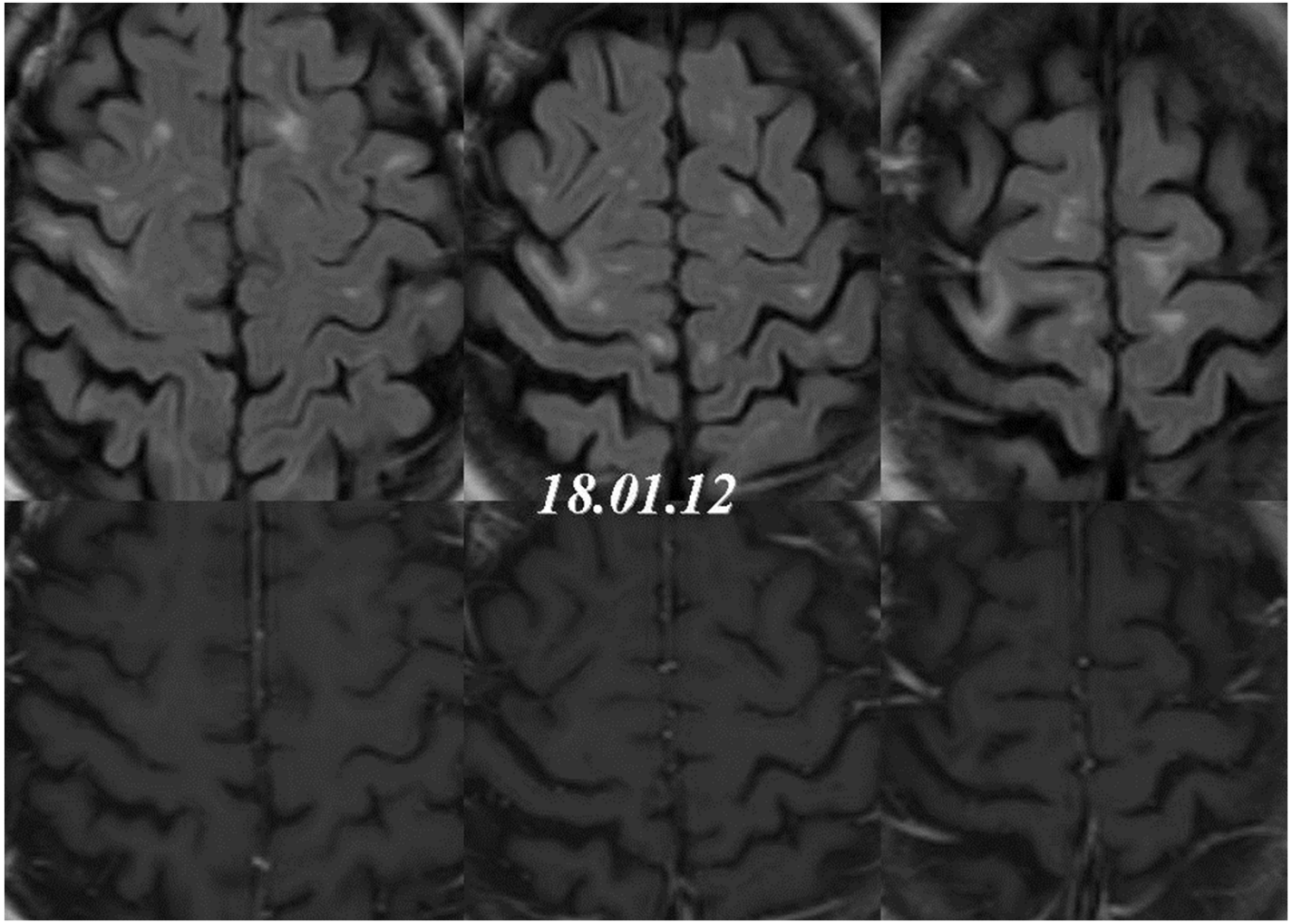
RM 18.01.12



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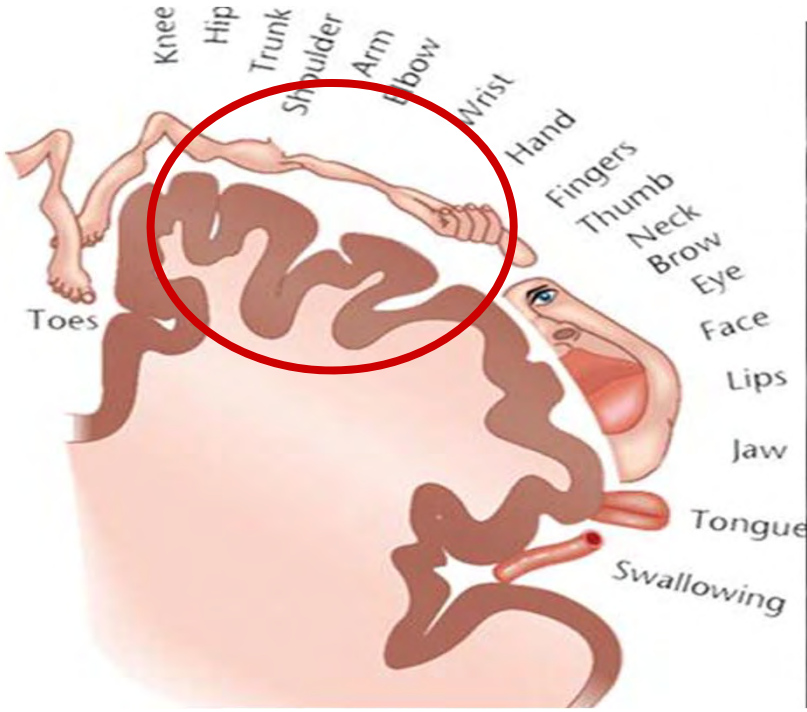
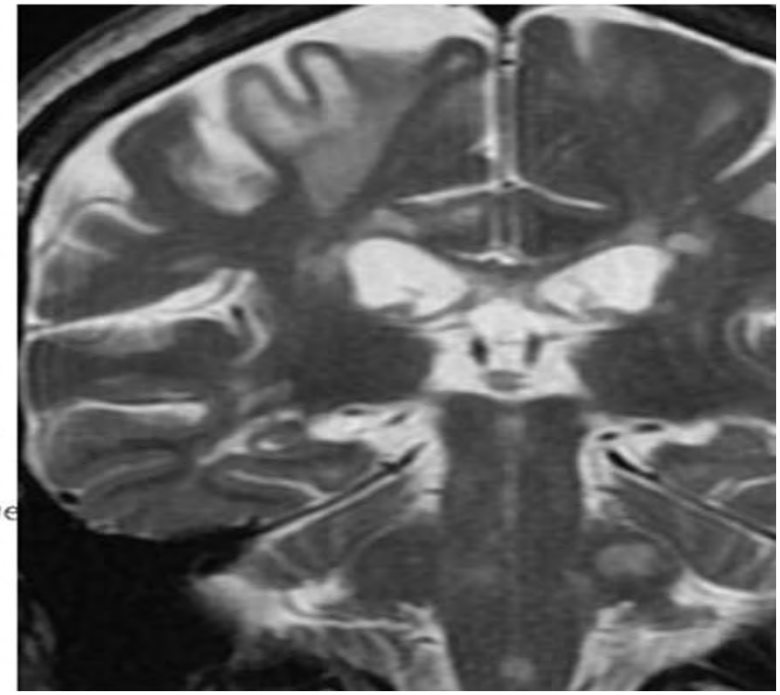
RM 18.01.12





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Ricovero

Puntura lombare per ricerca JCV:

negativa (4 laboratori)

Trattamento combinato:

- plasmaferesi
- mirtazapina (30mg/die)
- meflochina (250 mg/sett)