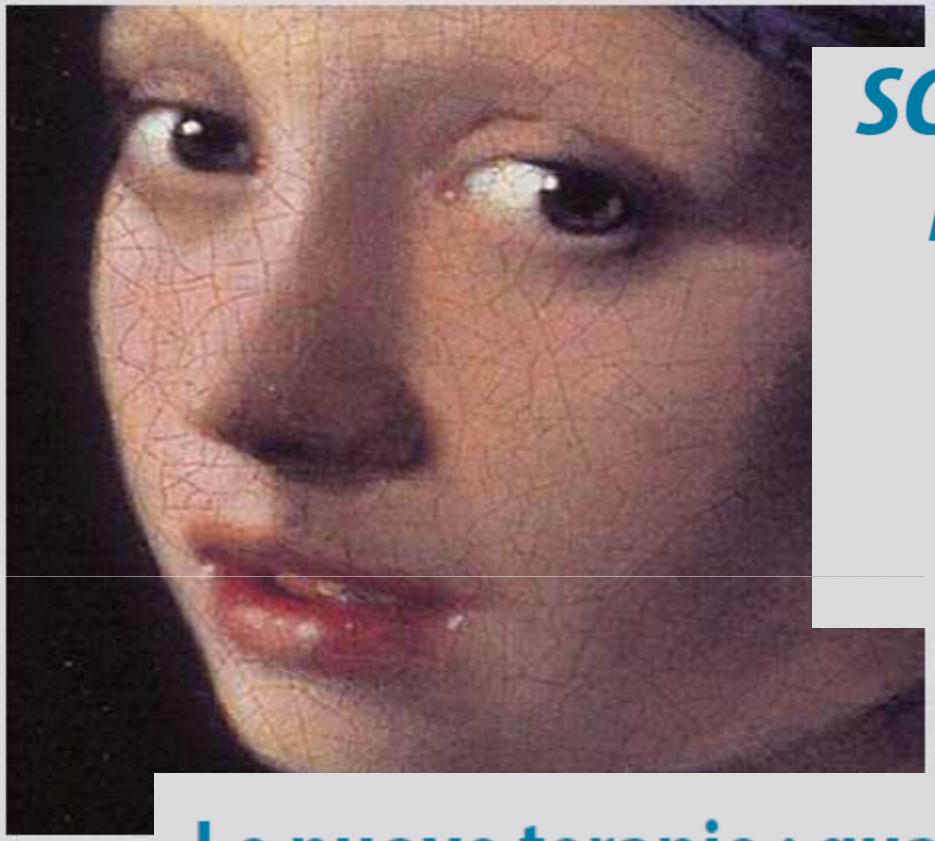


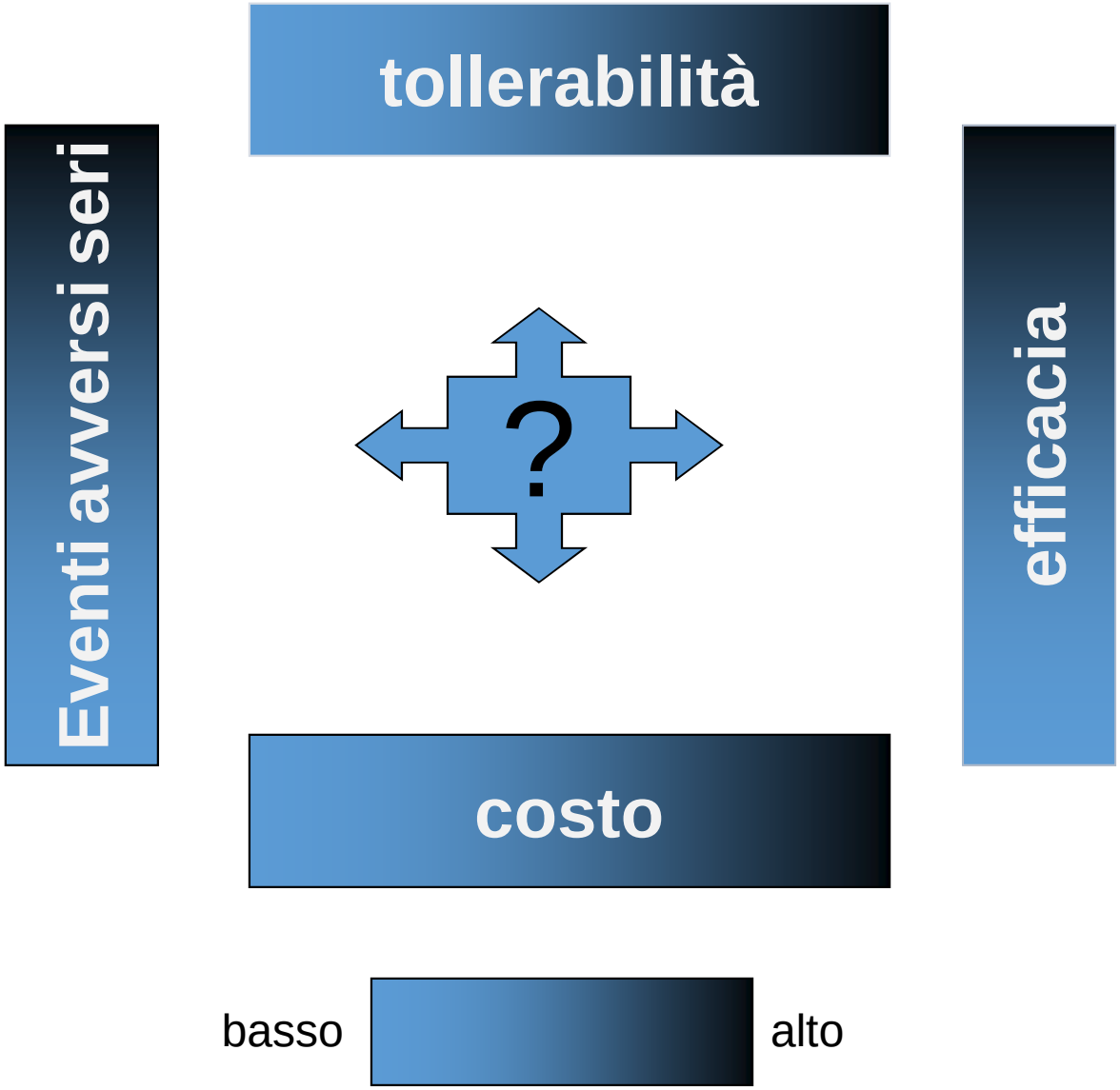
SCLEROSI MULTIPLA: il volto quotidiano della malattia

mercoledì 9 aprile 2014

ore 14:00 - 22:00

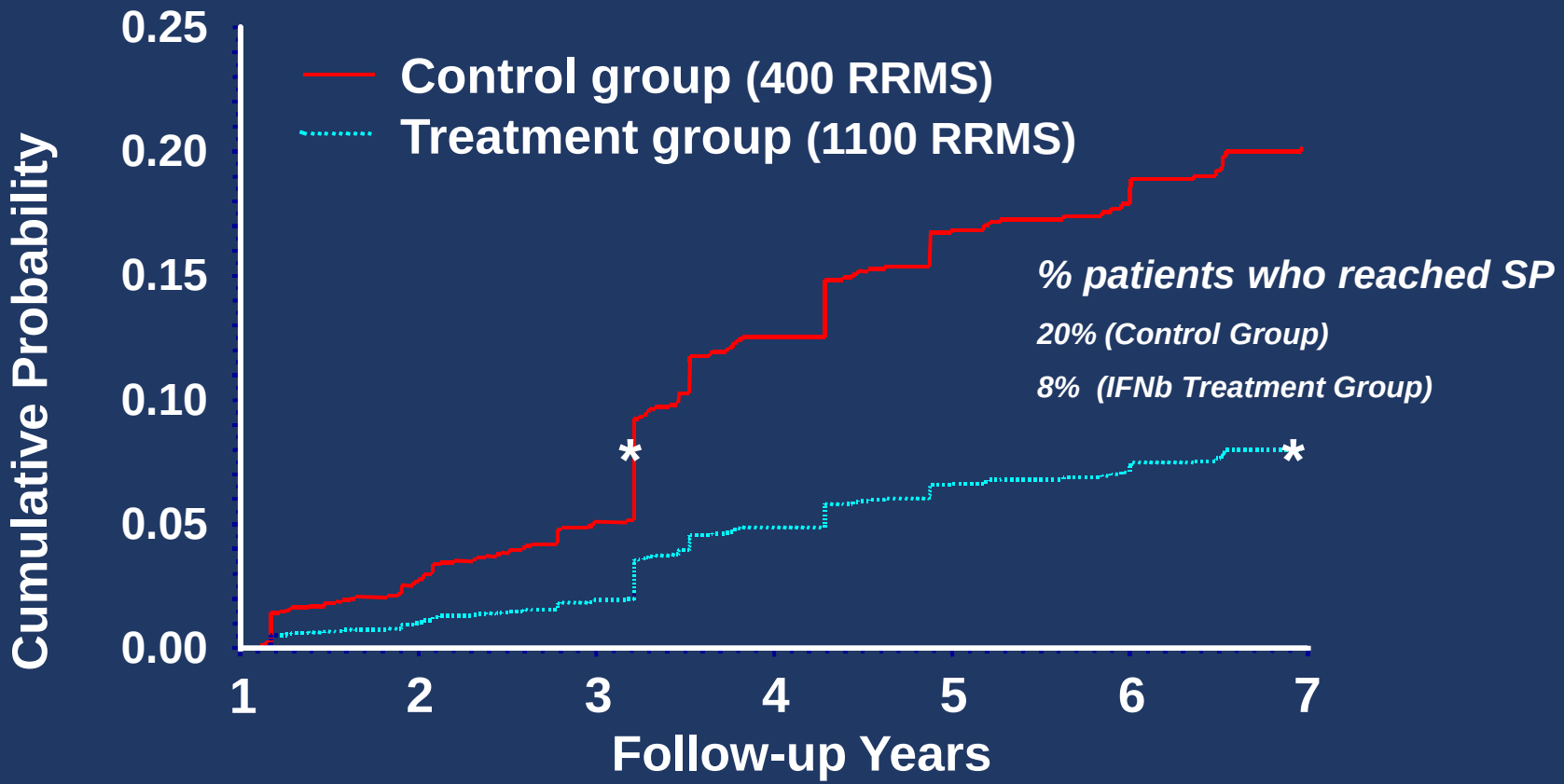
Le nuove terapie : quali promesse in termine di efficacia e sicurezza sono state rispettate ad oggi

A. Ghezzi


tollerabilità
Eventi avversi seri
?
efficacia
costo
basso
alto

Frequency of event		Detection
1:10	Very common (≥10%)	Development Programme
1:100	Common (1- <10%)	
1:1 000	Uncommon (0,1 - <1%)	
1:10 000	Rare (0,01 - <0,1%)	Post-Marketing Surveillance
1:100 000	Very rare (<0,01%) Not known (cannot be estimated from the available data)	
1:1 000 000		
1:10 000 000		

Propensity score-adjusted survival curves for endpoint: time from 1st visit to SP



* 8% threshold was reached in terms of time from the 1° visit to SP with a delay of 3.8 years (7 years for treated vs. 3.2 for untreated controls).

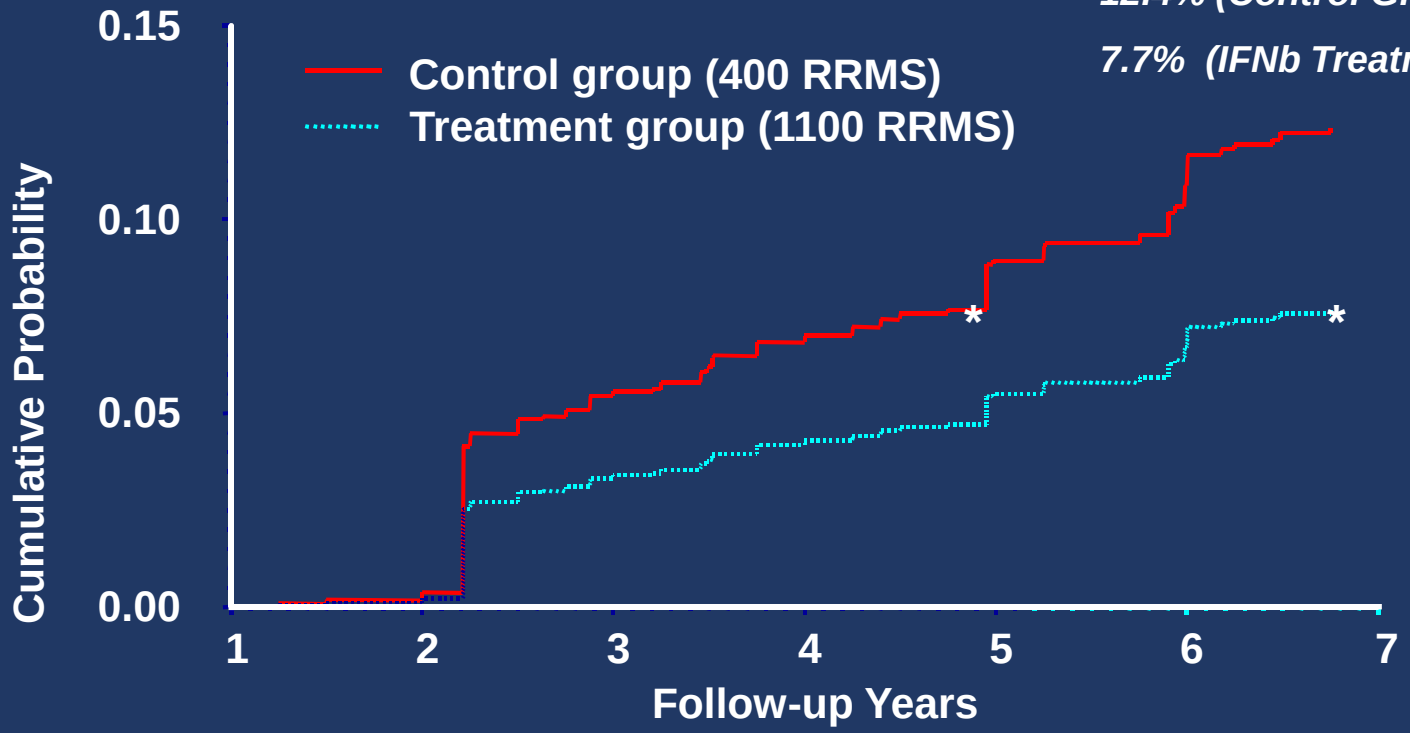
Trojano et al, Ann Neurol 2007

Propensity score-adjusted survival curves for endpoint: time from 1st visit to EDSS 6

20.1% of patients reached EDSS 6

12.4% (Control Group)

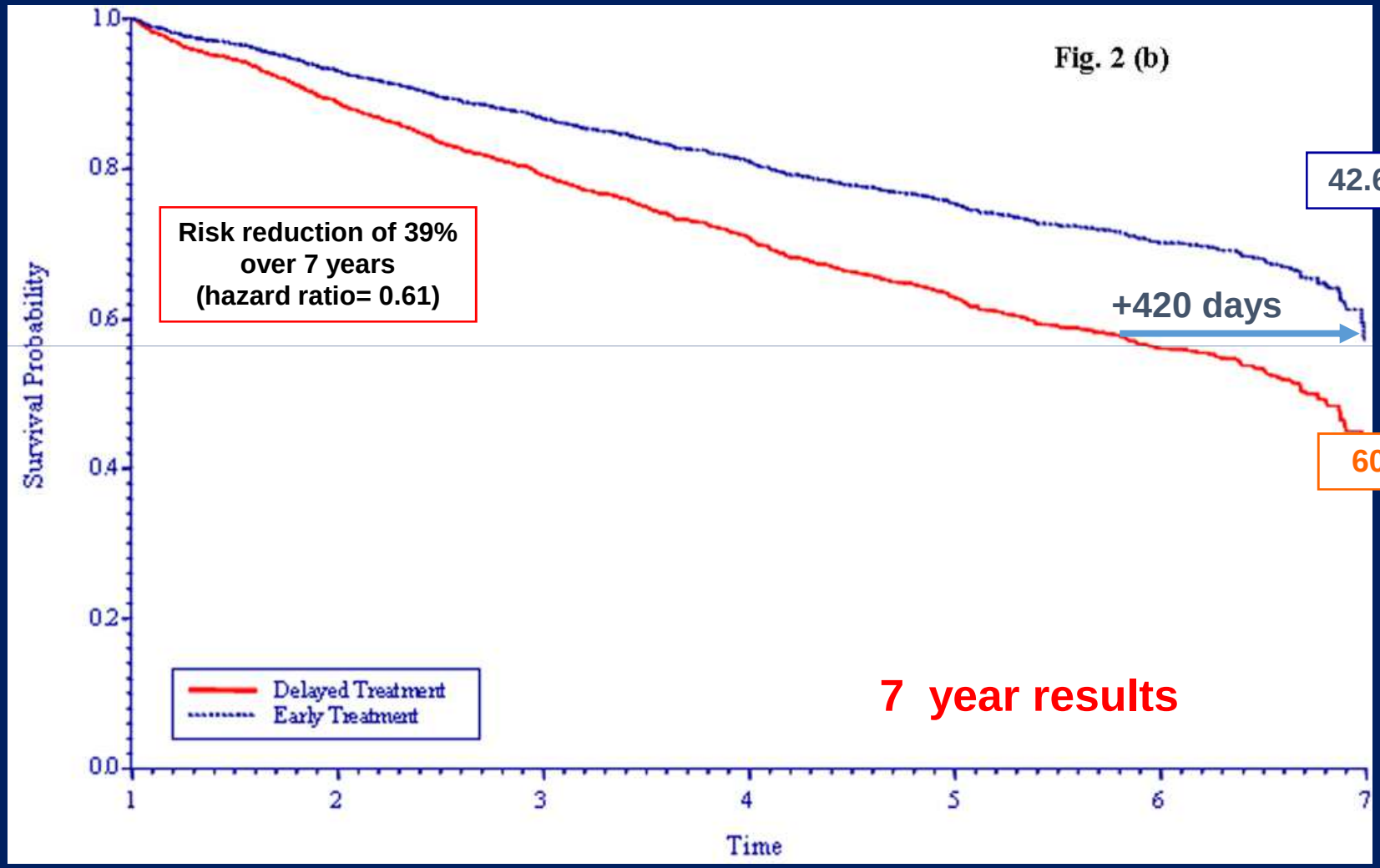
7.7% (IFNb Treatment Group)



* 7.7% threshold was reached in terms of time from the 1° visit with a delay of 2.2 years (7 years for treated vs. 4.8 for untreated controls).

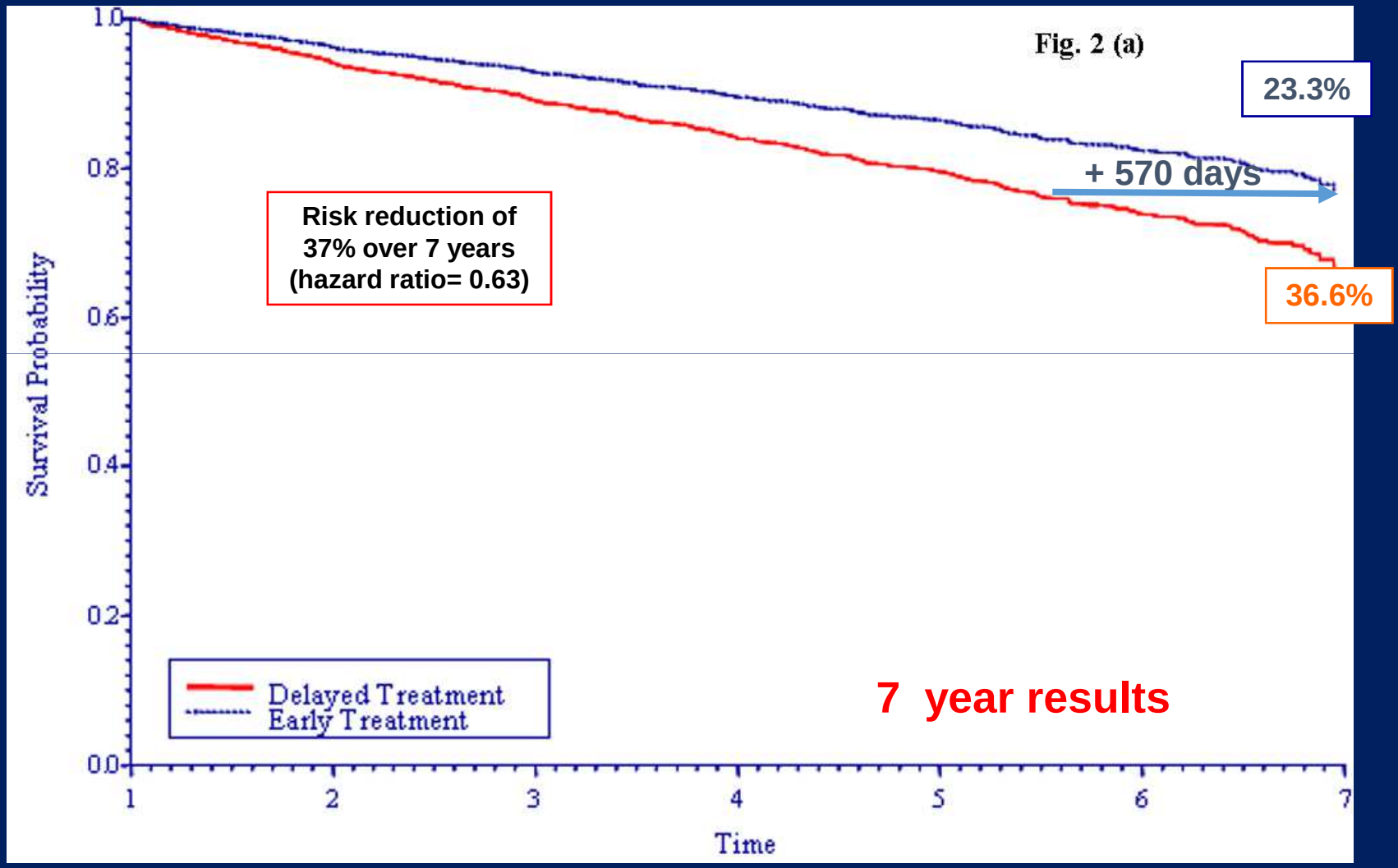
Trojano et al, Ann Neurol 2007

PS-adjusted survival curves for time from IFNβ initiation to reach 1-point EDSS progression in RR MS with "early" (within 1 year from onset) and "delayed" treatment (> 1 year from onset)



Trojano et al. Ann Neurol 2009

PS-adjusted survival curves for time from IFNβ initiation to reach EDSS 4 in RR MS with "early" (within 1 year from onset) and "delayed" treatment (> 1 year from onset)



Trojano et al. Ann Neurol 2009

Farmaci immunomodulanti di uso corrente

- Efficacia dimostrata nella real life

- Buona safety, non evidenza di eventi avversi severi

ma …

1- Eventi avversi seri a farmaci di uso corrente, più rari e meno noti

Renal thrombotic microangiopathy caused by interferon beta-1a treatment for multiple sclerosis

Julien Mahe[1]
Aurélie Meu
Anne Moreau
Caroline Ver
Pascale Jollie

Drug Design, Development and Therapy 2013:7 723–728

Makhani N, Ngan BY, Kamath BM, Yeh EA.
Glatiramer acetate-induced acute hepatotoxicity in an adolescent with MS.
Neurology 2013;81:850-2.

2- Eventi avversi seri a farmaci di uso corrente, evidenziati da studi di post-marketing

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

M. Martinelli, MD
E. Cocco, MD
R. Capra, MD
G. Salemi, MD
P. Gallo, MD
M. Capobianco, MD
L. Pesci, MD
A. Ghezzi, MD
C. Pozzilli, MD
A. Lugaresi, MD
P. Bellantonio, MD
M.P. Amato, MD
L.M. Grimaldi, MD
M. Trojano, MD
G.L. Mancardi, MD
R. Bergamaschi, MD
C. Gasperini, MD
M. Rodegher, MD
L. Straffi, MD
M. Ponzio, PhD
G. Comi, MD
for The Italian Mitoxantrone Group

ABSTRACT

Objectives: To evaluate the incidence and dose-dependency of mitoxantrone (MTX)-associated acute myelocytic leukemia (AML) in the network of Italian multiple sclerosis (MS) clinics.

Methods: We performed a multicenter retrospective cohort study of patients treated with MTX in MS centers under the Italian national health care system between 1998 and 2008. Demographic, disease, treatment, and follow-up information were collected using hospital records.

Results: Data were available for 3,220 patients (63% women) from 40 Italian centers. Follow-up (mean ± SD) was 49 ± 29 months (range 12–140 months). We observed 30 cases of AML (incidence 0.93% [95% confidence interval 0.60%–1.26%]). The mean cumulative dose was higher in patients with AML (78 vs 65 mg/m², $p = 0.028$). The median interval from the start of therapy to AML diagnosis was longer than expected at 33 months (range 13–84 months); 8 patients (27%) developed AML 4 years or more after the first MTX infusion. The rate of mortality associated with AML was 37%.

Conclusions: This higher than expected risk of AML and related mortality requires that treatment decisions must be made jointly between clinicians and patients who understand their prognosis, treatment options, and treatment-related risks. The now large exposed MS population must be monitored for hematologic abnormalities for at least 6 years from the end of therapy, to ensure the rapid actions needed for early diagnosis and treatment of AML. *Neurology® 2011;77:1-1*

GLOSSARY

AML = acute myelocytic leukemia; **APL** = acute promyelocytic leukemia; **CI** = confidence interval; **MS** = multiple sclerosis; **MTX** = mitoxantrone; **PML** = progressive multifocal leukoencephalopathy; **ROC** = receiver operating characteristic.

RESEARCH PAPER *Multiple Sclerosis 2008; 14: 1225–1233*

Frequency and risk factors of mitoxantrone-induced amenorrhea in multiple sclerosis: the FEMIMS study

*E Cocco[1], C Sardu[2], P Gallo[3], R Capra[4], MP Amato[5], M Trojano[6], A Uccelli[7], MG Marrosu[1] and the FEMIMS group**

3- Eventi avversi a farmaci di recente/imminente introduzione

RESEARCH PAPER

Efficacy and safety of natalizumab in multiple sclerosis: interim observational programme results

Helmut Butzkueven,[1,2] Ludwig Kappos,[3] Fabio Pellegrini,[4] Maria Trojano,[5] Heinz Wiendl,[6] Radhika N Patel,[7] Annie Zhang,[7] Christophe Hotermans,[7]
Sh
In

Results In this 5-year interim analysis, 4821 patients were enrolled. Follow-up for at least 4 years from natalizumab commencement in 468 patients and at least 2 years in 2496 patients revealed no new safety signals. There were 18 cases of progressive multifocal leucoencephalopathy reported, following 11–44 natalizumab infusions. Mean annualised relapse rate decreased from 1.99 in the 12 months prior to baseline to 0.31 on natalizumab therapy ($p<0.0001$), remaining low at 5 years. Lower annualised relapse rates were observed in patients who used natalizumab as first MS therapy, in patients with lower baseline EDSS scores, and in patients with lower prenatalizumab relapse rates. Mean EDSS scores remained unchanged up to 5 years.

Conclusions Interim TOP data confirm natalizumab's overall safety profile and the low relapse rate and stabilised disability levels in natalizumab-treated patients with RRMS in clinical practice.

Trial registration number NCT00493298.

Number of patients dosed with natalizumab, n (%)	4821 (100)
Number of patients who discontinued natalizumab,* n (%)	1222 (25.3)
Reasons for natalizumab discontinuation,† n (%)	
Anti-JCV antibody positive	277 (5.7)
Medication change‡	247 (5.1)
Insufficient efficacy	229 (4.8)
Patient decision	171 (3.5)
Withdrawal of consent	142 (2.9)
Adverse event (non-serious adverse event)	107 (2.2)
Physician decision	97 (2.0)
Pregnancy/pregnancy desire	74 (1.5)
Tolerability problem	65 (1.3)
Natalizumab treatment duration concern	65 (1.3)
Serious adverse event	51 (1.1)
Antibodies to natalizumab	44 (0.9)
Other reason	35 (0.7)
Non-compliance	31 (0.6)
Prior IS use	28 (0.6)
Safety concern	26 (0.5)
Lost to follow-up	24 (0.5)
PML§	7 (0.1)
Malignancy/cancer	7 (0.1)
Moved out of area	5 (0.1)
Inconvenience	5 (0.1)
Other serious infection	4 (<0.1)
No reason given in data	3 (<0.1)
Death	2 (<0.1)
Opportunistic infection	1 (<0.1)

Table 2 Continued

Number of patients enrolled in TOP	4821
Insufficient efficacy	46 (1.0)
Adverse event (non-serious adverse event)	43 (0.9)
Inconvenience	39 (0.8)
Serious adverse event	34 (0.7)
Other reason	32 (0.7)
Pregnancy/pregnancy desire	27 (0.6)
Natalizumab antibody positive	20 (0.4)
Non-compliance	13 (0.3)
Safety concern	11 (0.2)
Tolerability problem	8 (0.2)
Prior IS use	8 (0.2)
Death	2 (<0.1)
PML	2 (<0.1)
Other serious infection	2 (<0.1)
No reason given in data	2 (<0.1)
Malignancy/cancer	1 (<0.1)

Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring

Ludwig Kappos, David Bates, Gilles Edan, Mefkûre Eraksoy, Antonio Garcia-Merino, Nikolaos Grigoriadis, Hans-Peter Hartung, Eva Havrdová, Jan Hillert, Reinhard Hohlfeld, Marcelo Kremenchutzky, Olivier Lyon-Caen, Ariel Miller, Carlo Pozzilli, Mads Ravnborg, Takahiko Saida, Christian Sindic, Karl Vass, David B Clifford, Stephen Hauser, Eugene O Major, Paul W O'Connor, Howard L Weiner, Michel Clanet, Ralf Gold, Hans H Hirsch, Ernst-Wilhelm Radü, Per Soelberg Sørensen, John King

Evaluation).[10] Natalizumab is generally recommended for individuals who have not responded to currently available first-line disease-modifying therapy or who have very active disease.

The overall incidence of serious adverse events as ... recorded only rarely in the post-marketing setting.

L'incidenza complessiva di eventi avversi seri è rara …
… casi con grave sofferenza epatica (…) sono stati registrati solo raramente nel setting di post-marketing

Delayed infusion reactions (>2 h after ... serious herpes infections, including one fatal case of herpes encephalitis.[29,30]

Reazioni ritardate all'infusione sono rare ma osservate …
… onfezioni herpetiche si verificano più frequentemente (…) ma ci sono solo rari segnalazioni di infezioni serie

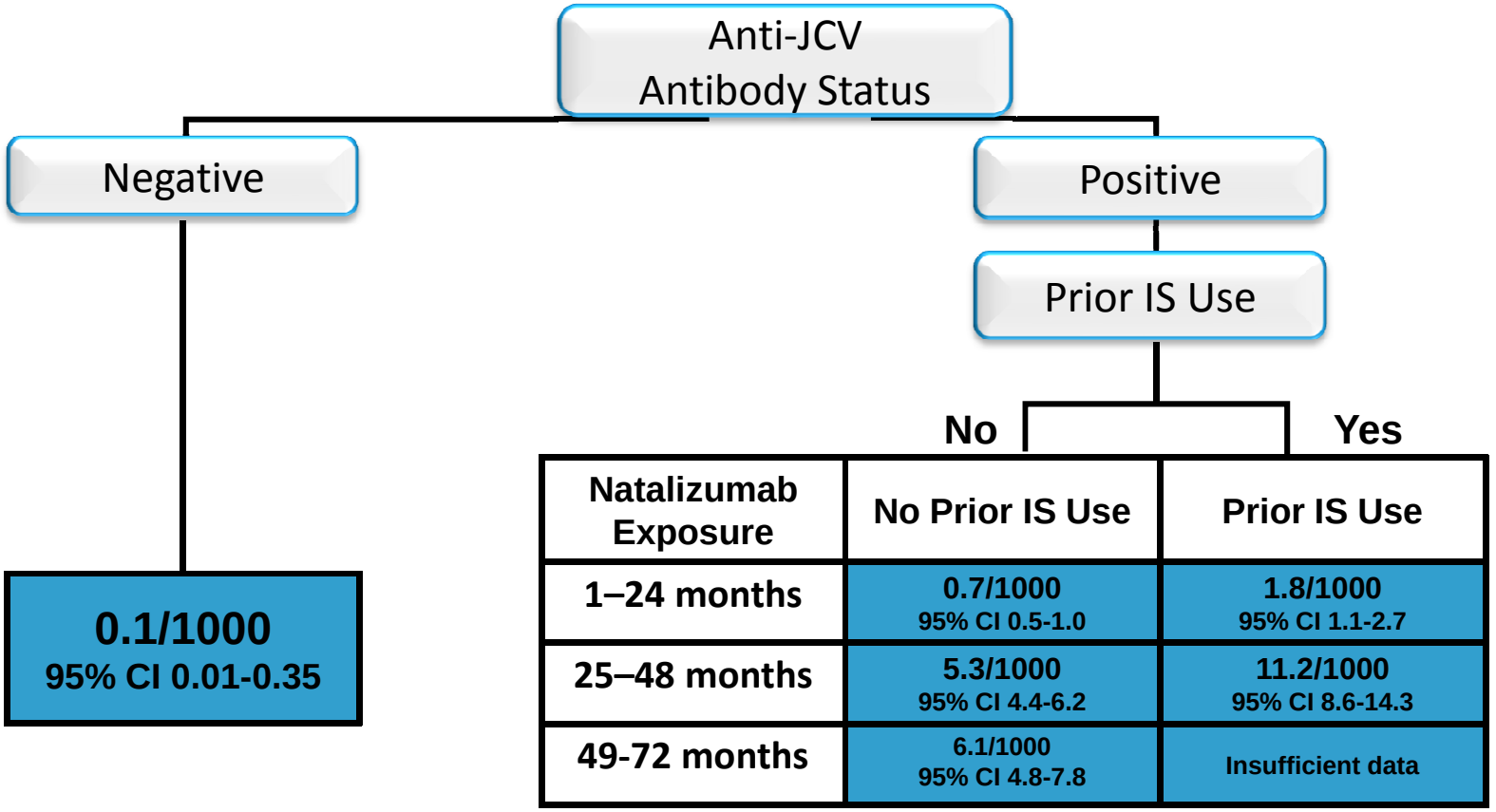
rate of potentially serious liver events noted thus far has been similar in the placebo and treatment arms of clinical studies of natalizumab. Cases of melanoma have been seen in women with MS treated with natalizumab.[31,32] However, a meta-analysis of safety data from clinical studies showed that the incidence of melanoma was similar in those who received natalizumab and placebo (0·07% *vs* 0·10%, corresponding to melanoma rates of ... typically present in immunosuppression-related CNS lymphoma.

Sono stati visti casi di melanoma (…) ma una meta-analisi ha dimostrato un'incidenza simile al placebo
… 2 casi di linfoma sono stati segnalati dopo 1 e 3 infusioni (pre-esistente)

L'evento più temibile è la PML

Eventi avversi seri e stratificazione del rischio

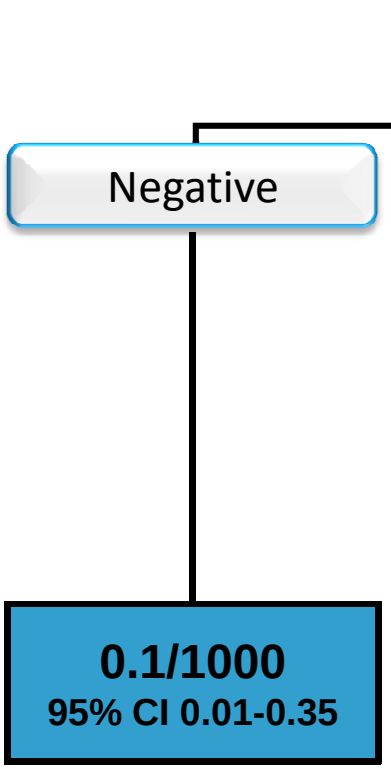
PML and NAT: rischio in relazione a durata trattamento, anticorpi anti-JCV, precedente immunosoppressione



Natalizumab Exposure	No Prior IS Use	Prior IS Use
1–24 months	0.7/1000 95% CI 0.5-1.0	1.8/1000 95% CI 1.1-2.7
25–48 months	5.3/1000 95% CI 4.4-6.2	11.2/1000 95% CI 8.6-14.3
49-72 months	6.1/1000 95% CI 4.8-7.8	Insufficient data

Eventi avversi seri e stratificazione del rischio

PML and NAT: rischio in relazione a durata trattamento, anticorpi anti-JCV, precedente immunosoppressione



Index	mesi 1-24	mesi > 24
< 0.9	0.1	0.3-0.4
0.9 – 1.5	0.1	0.7-1.3
> 1.5	1	8.1-8.3
prec. stime	0.6	5.2-5.4

NATALIZUMAB
Studi post-marketing per valutazione long-term di efficacia e sicurezza

	STRATA	TOUCH®	TYGRIS	TOP	Registro Gravidanze
Impegno con Autorità Regolatorie	●	●	●	●	●
Studio interventistico (IIIb)	●				
Obbligatorio per la prescrizione		●			
Programma osservazionale			●	●	●
Sicurezza: - Tutti i SAEs - Solo infezioni opport. - Status Ab anti-JCV	●	●	●	● ●	●
Efficacia (ricadute, EDSS)	●			●	
Numero di pazienti arruolabili: - controlli	~1.000	Illimitato	5.000	6.000 (●)	>300
Centri partecipanti	ROW	US	US+ROW	ROW	US+ROW
Durata (anni)	10	Illimitata	5	10	Illimitata

Gentilmente concessa da dott. Giannattasio, Biogen

I registri/studi osservazionali di fingolimod

PASS EU **Post-Authorization Safety Study** **Pazienti 2a linea**	**PASS USA** **Post-Authorization Safety Study** **Pazienti 1a linea**	**Gilenya Pregnancy Registry**	**PANGAEA** **(Post-Authorization Non-interventional German sAfety of GilEnyA in RR MS patients)**
Attivato in EU e in Usa per monitorare l'esposizione a lungo termine, fino a 5 anni, del trattamento con fingolimod. Previsto un arruolamento di circa 4000 pts fingolimod e 2000 in DMTs. L'esposizione totale ipotizzata sarà di 16.000 pazienti/anno		Lanciato in 10 nazioni. Sarà attivo per 6 anni e raccoglierà informazioni sull'esposizione a fingolimod in circa 500 gravidanze. Al 28 febbraio 2013, 15 gravidanze incluse.[1]	Attivato nel 2011 in Germania per stabilire la sicurezza e la tollerabilità di fingolimod nella pratica clinica e per indagarne gli aspetti farmacoeconomici. Il registro è aderente per struttura e contenuti all'RMP EMA. Al 31 luglio 2012 risultano arruolati 1819.[2]

Sono attivi molti registri su base nazionale o sub nazionale: «Pacific Northwest MS registry» ; «US Department of Defence Database» di cui non sono ancora disponbili i dati

[1]: Hellwig. Poster n. TBD ECTRIMS 2013; [2]: Ziemssen. Poster n. 522 ECTRIMS 2012

FINGOLIMOD, DATI DI POSTMARKETING

Aree di sorveglianza e di attenzione

1- Infezioni

- **Caso ulteriore di riattivazione erpetica**
- **Caso di PML**

2- Ambito cardiovascolare

- **Non ulteriori elementi di rilevanza in ambito cardiovascolare**

3- edema maculare

4- Altri eventi rari e imprevedibili: sindrome emofagocitaria

Eventi avversi seri e stratificazione del rischio
Fingolimod e sorveglianza di post-marketing

Fingolimod: caso con evoluzione viscerale fatale per riattivazione da varicella-virus

Highlights from Expert Panel Meeting I
Incidence rates and severity with 73.000 patient years exposure

- The rate of Varicella Zoster Virus (VZV) infections with fingolimod 0.5 mg in clinical trials is higher than with placebo. In both groups, the incidence was considered low.
- Serious or complicated events of VZV are uncommon, visceral involvement is rare
- The current fatal case with visceral involvement was deemed a re-activation that occurred in the context of concomitant steroid use with fingolimod 0.5 mg
- Infectious disease experts conveyed that severe, fatal cases of primary varicella (chickenpox) or reactivation (zoster) can occur during corticosteroid treatment

Highlights from Expert Panel Meeting II
Corticosteroid use

- Based on the available clinical trial data, a clear relationship of concomitant corticosteroid use and risk of VZV (during and within 30 days) cannot be established
  - only 1 case of VZV infection occurred on fingolimod 0.5 mg after steroid use
- Current data do not support routine use of prophylaxis in all patients receiving short course of corticosteroids
  - in clinical trials, steroid use was restricted to 3-5 days
- Antiviral prophylaxis may be considered when longer duration of corticosteroid use is prescribed, or in high risk patients, e.g. elderly, family history, etc.

Highlights from Expert Panel Meeting III
Immunity and risk mitigation

- Immunity to varicella (chickenpox) needs to be established prior to Gilenya treatment by a HCP confirmed history of chickenpox or documentation of a full course of vaccination with varicella vaccine
- Presence of VZV antibodies reflect previous exposure to varicella (chickenpox), either through primary infection or vaccination
- Antibody titers do not predict protection from zoster reactivation or dissemination; repeated measurement of VZV antibody titers is not informative and thus not recommended

Fingolimod: caso con PML?

- 46 year old diagnosed with MS in early 2012. In retrospect the case was unusual from beginning, “relapses” were accompanied by severe headaches, nausea and emesis.
- Initially there were few unspecific lesions on MRI and there were no oligoclonal bands in CSF
- There was no evidence for other conditions impacting the immune system (HIV, Tb, sarcoidosis); no antiphospholipid antibodies or antinuclear antibodies
- Testing for other CNS infections than JC virus was negative including borrelia, treponema, varicella, and toxoplasma.
- Based on assessments of MR images and repeated negative results of anti-aquaporin 4 antibodies, this is not a case of NMO.
- She received interferon and azathioprine for one month before she was started on Gilenya in Nov 2012.
- On last MRI pre-Gilenya in Oct 2012, expert MRI reviewers found the MRI lesions present to be atypical and could not exclude PML.
- The patient had experienced approximately 9 relapses over 1 year with progression of disability (EDSS 8 in June 2013).
- Relapses were typically treated with high dose IV Methylprednisolone for 5 days followed by oral tapering
- A CSF sample tested in Oct 2012 was negative (commercial assay). Serum JCV antibody status is not available.
- During treatment with Gilenya the patient worsened and a decision was made to refer her for a BMT. Gilenya was discontinued on June 20, 2013
- Lymphocyte counts on admission in the hospital (approx. 2 weeks after discontinuation of Gilenya) were normal. Lymphocyte counts while on Gilenya are not available.
- When she was admitted to the hospital for a BMT, on June 25, 2013 she was tetraplegic and unconscious. CSF tested for viruses and found to be positive for JCV PCR (371 copies/ml), confirmed in additional test.
- Her current clinical condition is largely due to extensive brainstem lesions
- The patient's condition was reported as slightly improved, she was still hospitalized at the latest report.

NOTA INFORMATIVA IMPORTANTE CONCORDATA CON LE AUTORITÀ

REGOLATORIE EUROPEE E L'AGENZIA ITALIANA DEL FARMACO (AIFA)

11/11/2013

Sindrome emofagocitica (*Haemophagocytic syndrome*, HPS) segnalata in pazienti trattati con fingolimod (Gilenya)

Gentile Dottoressa, Egregio Dottore,

L'Agenzia Italiana del Farmaco (AIFA) in accordo con l'Agenzia europea dei medicinali e Novartis desidera informarLa in merito a due episodi fatali di sindrome emofagocitica segnalati in pazienti con sclerosi multipla trattati con fingolimod.

Riassunto

- Due casi fatali di sindrome emofagocitica (*haemophagocytic syndrome*, HPS), entrambi insorti nel contesto di un'infezione, sono stati segnalati in pazienti trattati con fingolimod 0,5 mg/die rispettivamente per 9 e 15 mesi.
- Una diagnosi precoce dell'HPS è importante per migliorare la prognosi, dando inizio tempestivamente al trattamento dell'HPS e della condizione sottostante, come ad esempio un'infezione virale.
- I segni e i sintomi frequentemente associati alla HPS sono:
    - febbre, astenia, epatosplenomegalia e adenopatia che possono essere associate a manifestazioni più gravi quali insufficienza epatica o distress respiratorio
    - citopenia progressiva, livelli di ferritina sierica marcatamente elevati, ipertrigliceridemia, ipofibrinogenemia, coagulopatia, citolisi epatica e iponatriemia.

nuovi farmaci

Agents	Route and dose	Presumed mechanism of action	Adverse events
Monoclonal antibodies Alemtuzumab [Coles *et al.* 2008; Cossburn *et al.* 2011]	12 or 24 mg i.v., 5 days consecutively initially, followed by 12 mg i.v., 3 days consecutively 1 year later	Anti- CD52 antibody Prolonged suppression of CD4+ T cells	Acute cell lysis with cytokine release syndrome Autoimmune thyroid disorders (Graves disease) Immune thrombocytopaenic purpura (including one fatal case) Goodpasture's syndrome Common infections (upper respiratory and urinary tract infections, herpes zoster after reactivation of varicella zoster virus) Vitiligo, bullous skin rash Possibly increased incidence of secondary malignancies
Rituximab [Hauser *et al.* 2008; Naismith *et al.* 2010]	375 mg/m² i.v. weekly × 4 weeks	Anti -CD20 monoclonal Ab Circulating B-cell depletion Reduced antigen Presentation	Infusion-related: fever, chills and occasional hypotension, dyspnoea Infection PML (only seen in combination with immunosuppressants in two patients with SLE) Systemic inflammatory syndrome
Ocrelizumab [Kappos *et al.* 2011]	600 or 2000 mg i.v., 2 weeks apart initially, followed by 600 mg, 1000 mg or placebo on weeks 24 and 26	Anti- CD20 monoclonal Ab	Serious opportunistic infections (including fatal cases) (from a phase III rheumatoid arthritis trial in combination with immunosuppressants) Common infections: influenza-like illness, upper respiratory and urinary tract infections, nasopharyngitis.
Ofatumumab [Taylor *et al.* 2011]	100, 300 or 700 mg, in two treatment courses (2 × 2 i.v. infusions)	IgG1kappa lytic monoclonal Ab, inducing a potent B-cell lysis	Rash and urticaria Angioedema Fatal interstitial lung disease Diarrhoea and pneumonia Pericardial effusion (from a study in patients with active rheumatoid arthritis)
Daclizumab [Wynn *et al.* 2010]	2 mg/kg subcutaneously every 2 or 4 weeks, for 24 weeks	interleukin-2 Rα antibody Anti-CD25 antibody	Serious skin rash Serious infections Liver function test abnormalities Fatal autoimmune hepatitis *In situ* breast carcinoma

nuovi scenari terapeutici: conoscenza rischi

S. Tenembaum

Ther Adv Neurol Disord

(2012) 5(3) 139–146

Eventi avversi a farmaci iniettivi (sintesi)

alemtuzumab	**Tiroidite autoimmune di Graves** **Citolisi acuta con sindrome da release di citochine** **Porpora trombocitopenica** **Sindrome di Goodpasture** **Infezioni, riattivazioni erpetiche** **Rash cutaneo bolloso** **Neoplasie?**
rituximab	Febbre infusion related Infezioni PML Sindrome infiammatoria sistemica
ocrelizumab	Infezioni opportunistiche serie (inclusi casi fatali) infezioni
daclizumab	Rash cutaneo serio Infezioni Epatopatia Epatite acuta fulminante neoplasie

nuovi

farmaci

Agents	Route and dose	Presumed mechanism of action	Adverse events
Oral therapies [Killestein *et al.* 2011]			
BG-12 (dimethyl fumarate)	240 mg twice a day, or three times a day	Induces activation of the nuclear factor E2-related factor-2 pathway Neuroprotection via NF_k B pathway Drug-induced shift towards a more anti-inflammatory cytokine profile (Th2) and adhesion molecule expression	Facial flushing Headache Gastrointestinal side effects
Fingolimod (FTY720) [Cohen and Chun, 2011; Khatri *et al.* 2011]	0.5 mg once daily	Sphingosine-1-phosphate receptor modulator Immune cell sequestration	Lymphocytopaenia Cardiac disorders (bradycardia, atrioventricular conduction block, hypertension) Common infections (nasopharyngitis) Serious infections (exacerbation of herpes virus infection, including two fatal cases) Macular oedema Hepatoxicity Back pain Possible increased incidence of secondary malignancies (localized skin cancers and ovarian cancer)
Laquinimod	0.6 mg daily	Immunomodulatory Derivative of linomide Induces a cytokine shift towards T-helper-2 and Th3 cytokines	Liver enzyme elevation (transient, asymptomatic) Gastrointestinal symptoms Back pain, arthralgia Possible venous thrombosis
Teriflunomide	7 or 14 mg daily	Active metabolite of leflunomide Inhibitor of pyrimidine synthesis by reducing the activity of mitochondrial enzyme dihydro-orotate dehydrogenase	Hepatotoxicity (fatal liver failure with leflunomide) PML (in a patient with SLE with leflunomide) Common infections Headaches Alopecia Rhabdomyolysis Teratogenic effects of leflunomide

Ab, antibody; i.v., intravenous; PML, progressive multifocal leucoencephalopathy; SLE, systemic lupus erythematosus.

nuovi

scenari

terapeutici:

conoscenza

rischi

S. Tenembaum

Ther Adv Neurol Disord

(2012) 5(3) 139–146

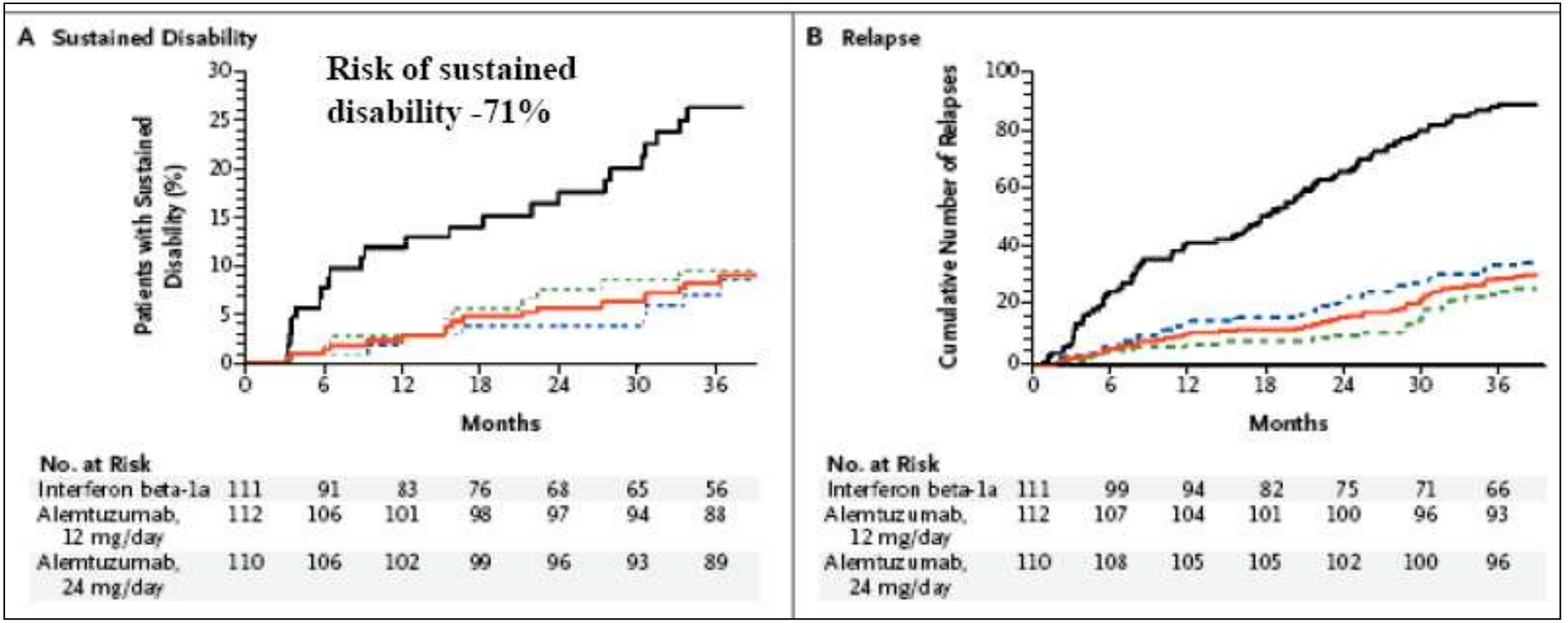
Eventi avversi a farmaci orali (sintesi)

BG12	**Flushing** **Cefalea** **Effetti gastrointestinali** **PML?**
fingolimod	Linfopenia Bradicardia Infezioni Infezioni erpetiche Edema maculare Tossicità epatica Neoplasie?
teriflunomide	Epatotossicità PML (in soggetto con LES e leflunomide) Cefalea Alopecia Rabdomiolisi Effetto teratogeno

ALEMTUZUMAB

Alemtuzumab vs IFNB 44ug x3

CAMMS 223



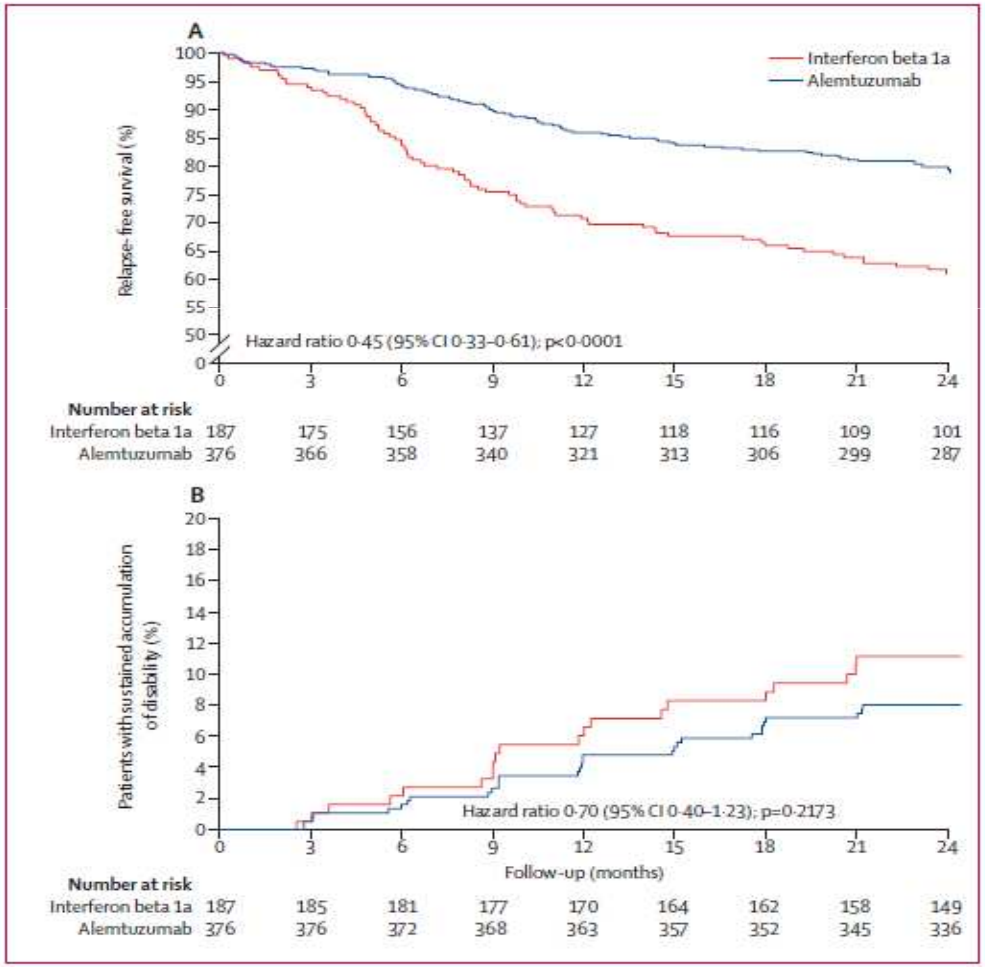
No. at Risk							
Interferon beta-1a	111	91	83	76	68	65	56
Alemtuzumab, 12 mg/day	112	106	101	98	97	94	88
Alemtuzumab, 24 mg/day	110	106	102	99	96	93	89

No. at Risk							
Interferon beta-1a	111	99	94	82	75	71	66
Alemtuzumab, 12 mg/day	112	107	104	101	100	96	93
Alemtuzumab, 24 mg/day	110	108	105	105	102	100	96

Coles et al. N Engl J Med 2008;359:1786-801.

Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet. 2012 Nov 24;380(9856):1819-28.*

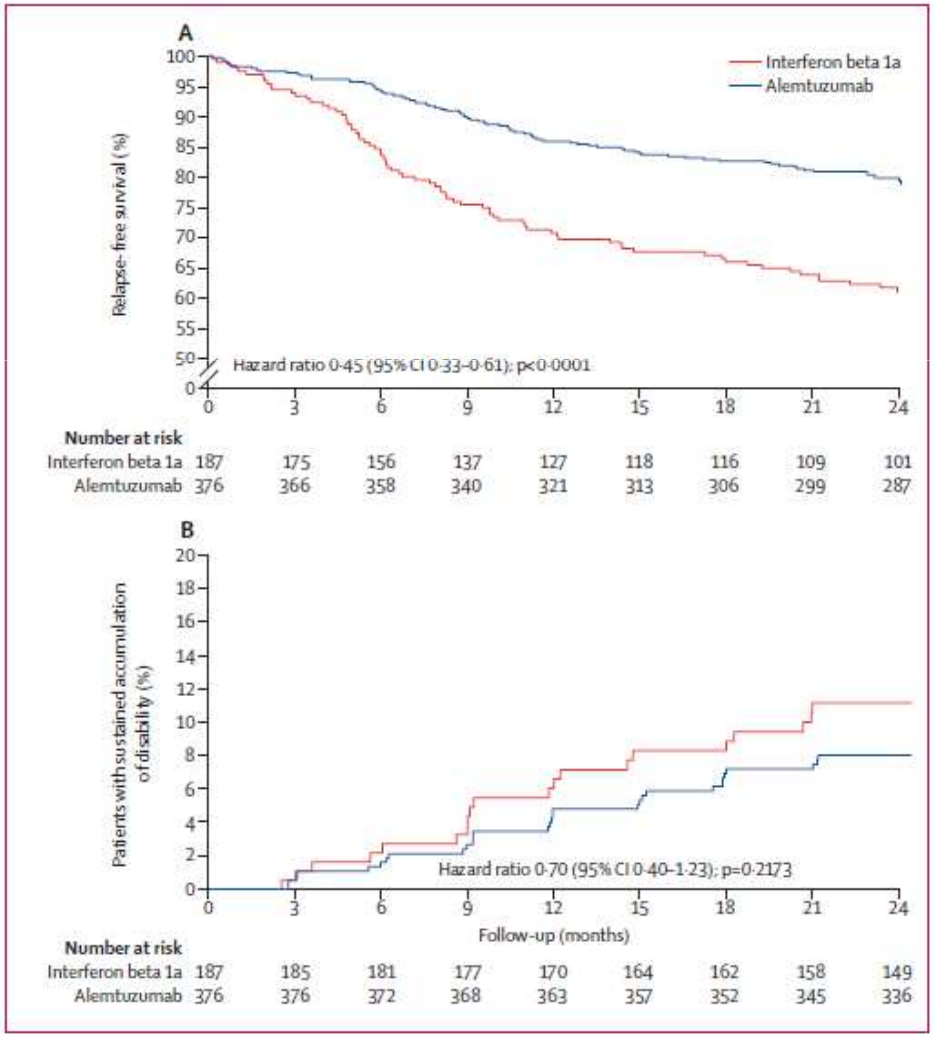
Studio CARE-MS1, di fase III, 563 pz randomizzati 1:2:2 a IFNb1a 44 mcg x 3/sett o Alemtuzumab 12 mg die o 24 mg die, follow-up di 24 mesi. Pazienti naive a una terapia per la SM.



54.9%

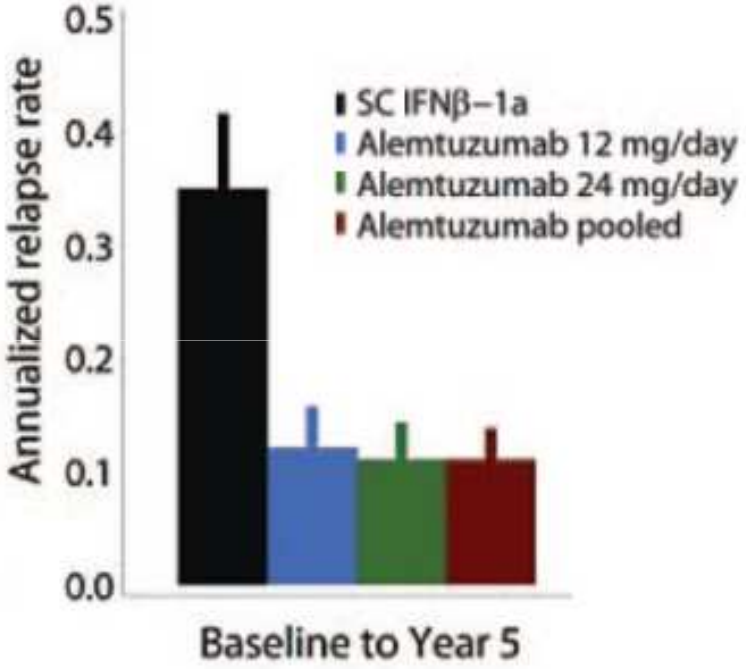
Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. ***Lancet. 2012 Nov 24;380(9856):1829-39.***

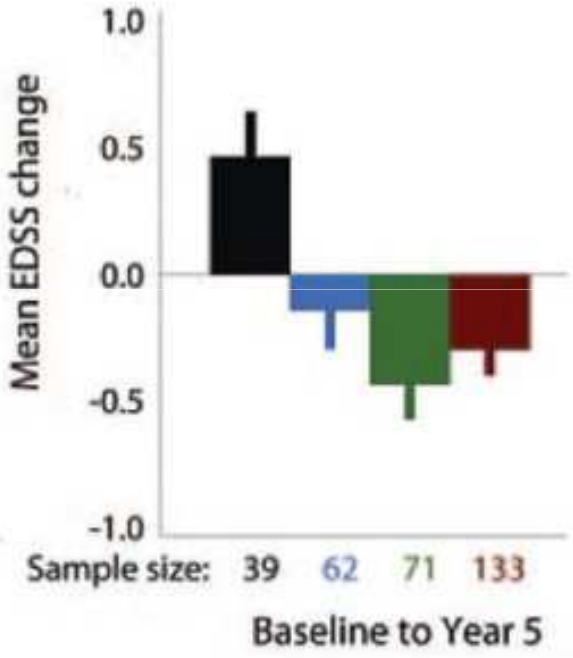
Identico al CARE-MS1 ma inclusi 628 pazienti che già avevano effettuato una terapia di I linea per la SM



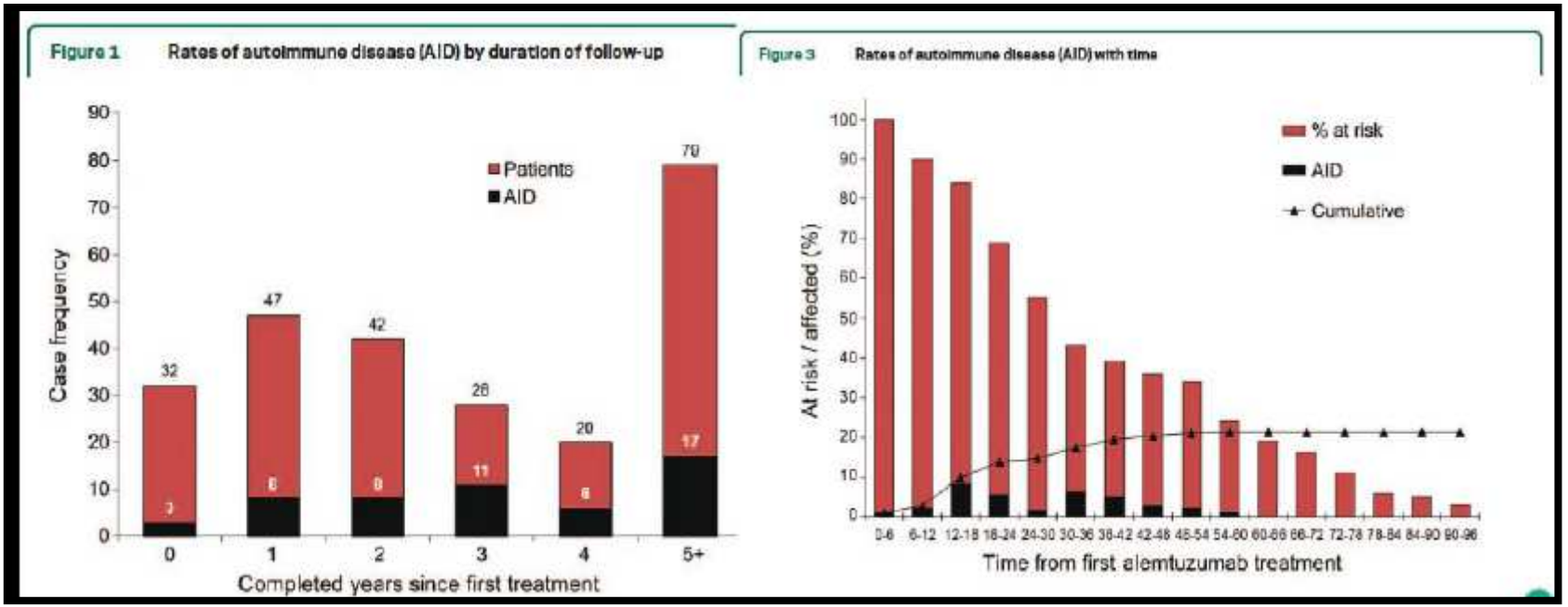
49.4%

42%


Annualized relapse rate
0.5
0.4
0.3
0.2
0.1
0.0
SC IFNβ–1a
Alemtuzumab 12 mg/day
Alemtuzumab 24 mg/day
Alemtuzumab pooled
Baseline to Year 5


Mean EDSS change
1.0
0.5
0.0
-0.5
-1.0
Sample size: 39 62 71 133
Baseline to Year 5

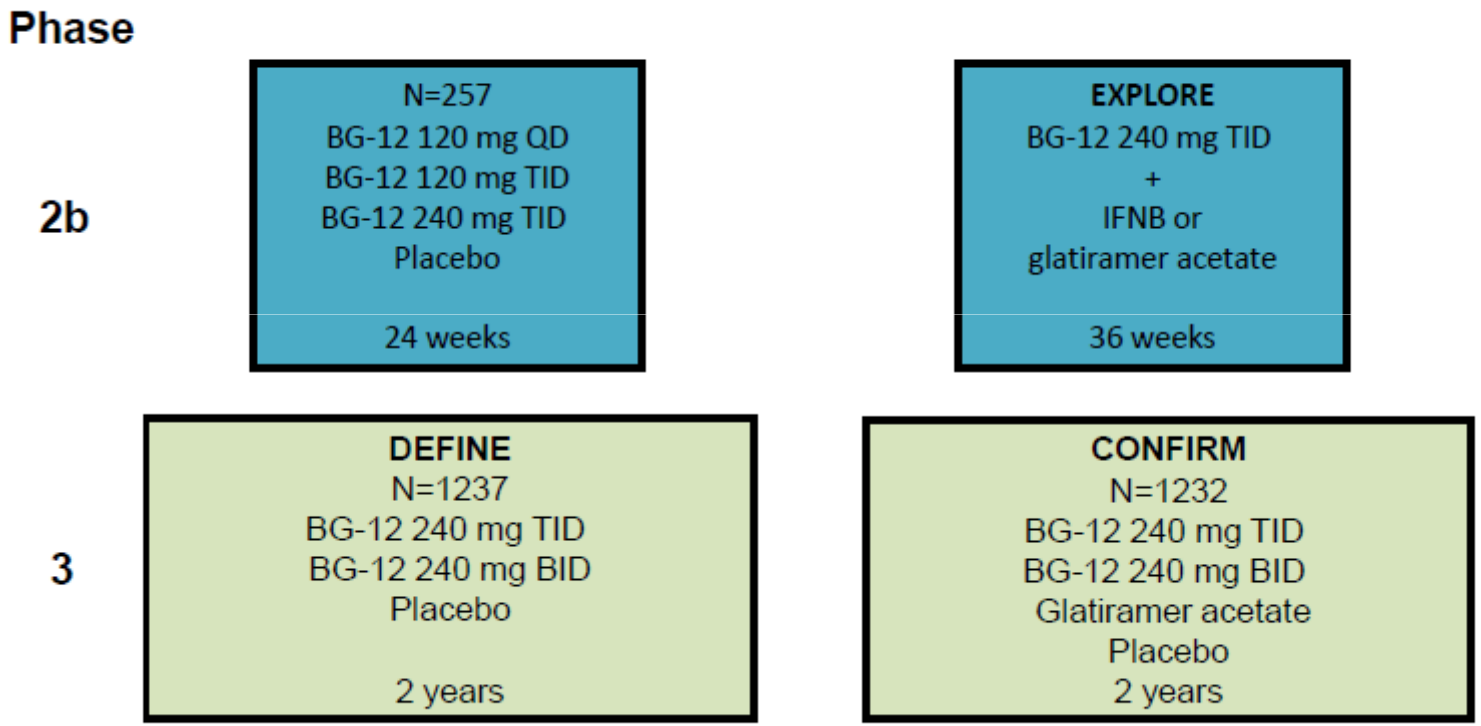
Incidence of Autoimmunity, n (%)	Alem 12 mg n=1216	Alem 24 mg n=269	Alem Pooled n=1485
Thyroid			
Patients with thyroid AEs	281 (23.1)	86 (32.0)	367 (24.7)
Hyperthyroidism	149 (12.3)	58 (21.6)	207 (13.9)
Hypothyroidism	123 (10.1)	31 (13.1)	154 (10.4)
Goiter	19 (1.6)	7 (2.6)	26 (1.8)
Thyroid mass	2 (0.2)	0	2 (0.1)
Thyroid disorder[a]	2 (0.2)	0	2 (0.1)
Laboratory investigations	63 (5.2)	21 (7.8)	84 (5.7)
SAEs	17 (1.4)	6 (2.2)	23 (1.5)
Immune thrombocytopenia			
Platelet- or AE-based definition[b]	13 (1.1)	9 (3.3)	22 (1.5)
AE-based definition	9 (0.7)	8 (3.0)	17 (1.1)
SAEs	7 (0.6)	5 (1.9)	12 (0.8)
Other autoimmune cytopenias			
Autoimmune pancytopenia	1 (0.1)	0	1 (0.1)
Hemolytic anemia	2 (0.2)	0	2 (0.2)
Nephropathies			
Anti-glomerular basement membrane glomerulonephritis	1 (0.1)	0	1 (0.1)
Glomerulonephritis membranous	1 (0.1)	0	1 (0.1)
Goodpasture's syndrome[c]	1 (0.1)	0	1 (0.1)



Sorveglianza a lungo termine – AEs fino a 5 anni

AE	Analysis	When	Follow-up
ITP	Complete blood count	Every month starting from the beginning of therapy	Test must continues on a monthly bases until 4 years after last infusion
Nephropathies	Serum creatinine, urinalysis and microscopy	Every month starting from the beginning of therapy	Tests must continues on a monthly bases until 4 years after last infusion
Thyroid	Thyroid function test	Every three months starting from the beginning of therapy	Every three months until 4 years after last infusion

BG12
Evidenze cliniche

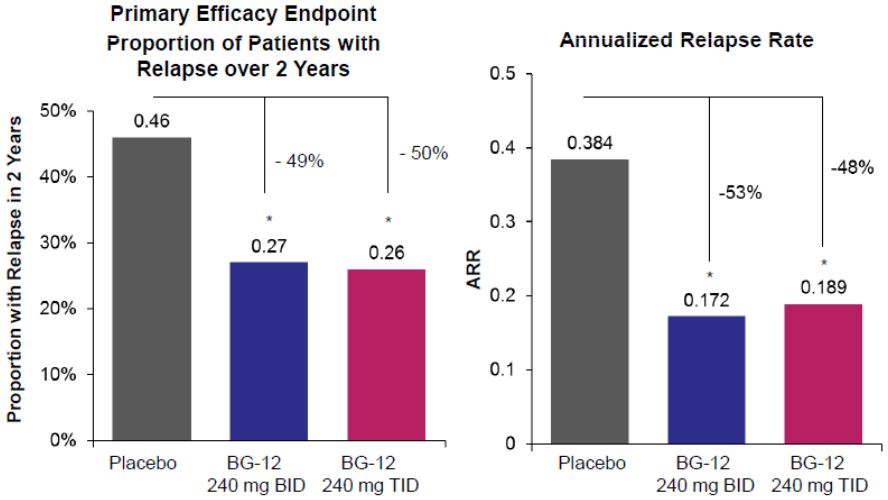


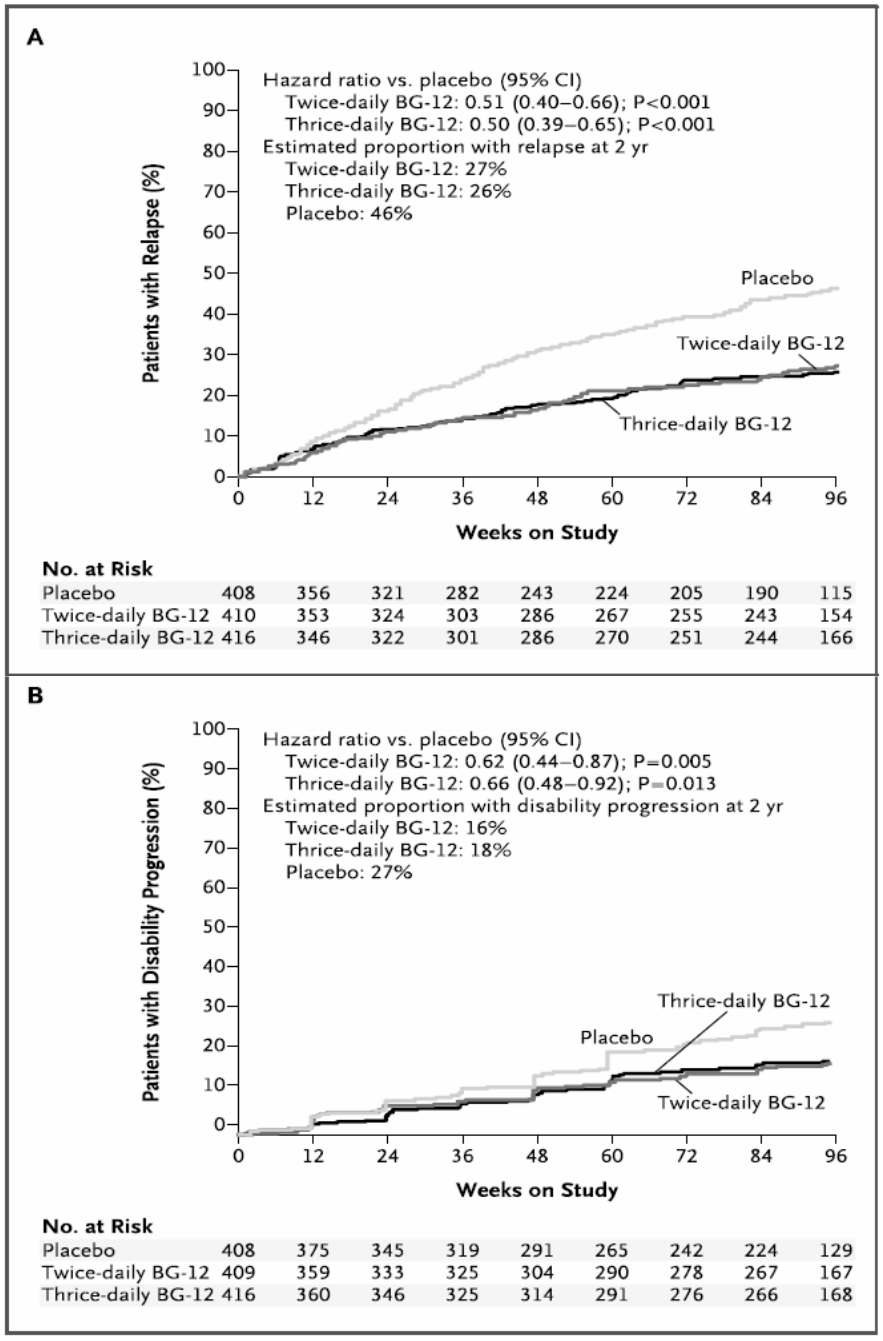
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Placebo-Controlled Phase 3 Study of Oral BG-12 for Relapsing Multiple Sclerosis

Ralf Gold, M.D., Ludwig Kappos, M.D., Douglas L. Arnold, M.D., Amit Bar-Or, M.D., Gavin Giovannoni, M.D., Krzysztof Selmaj, M.D., Carlo Tornatore, M.D., Marianne T. Sweetser, M.D., Ph.D., Minhua Yang, M.S., Sarah I. Sheikh, M.D., and Katherine T. Dawson, M.D., for the DEFINE Study Investigators*



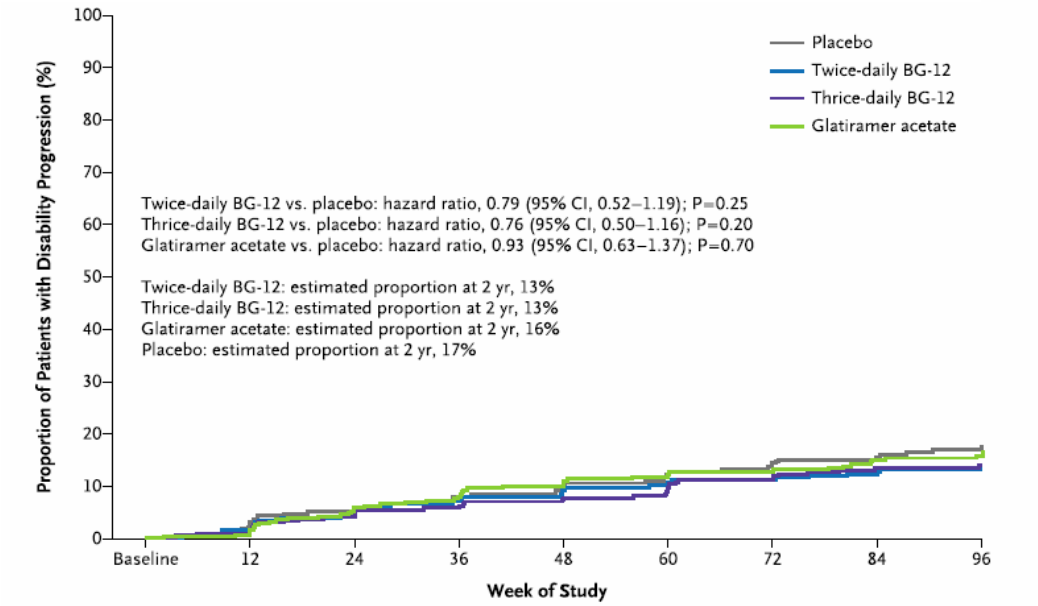


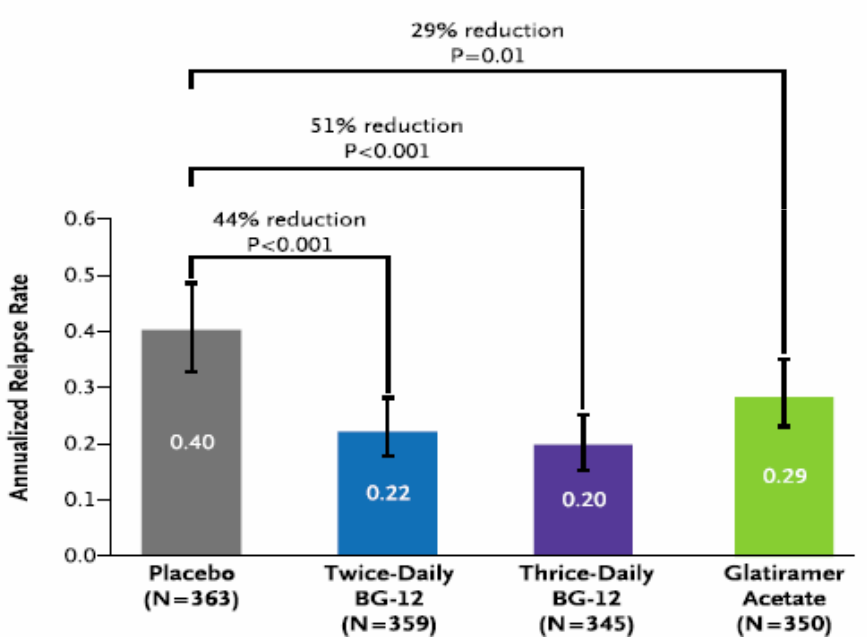
The NEW ENGLAND JOURNAL of MEDICINE

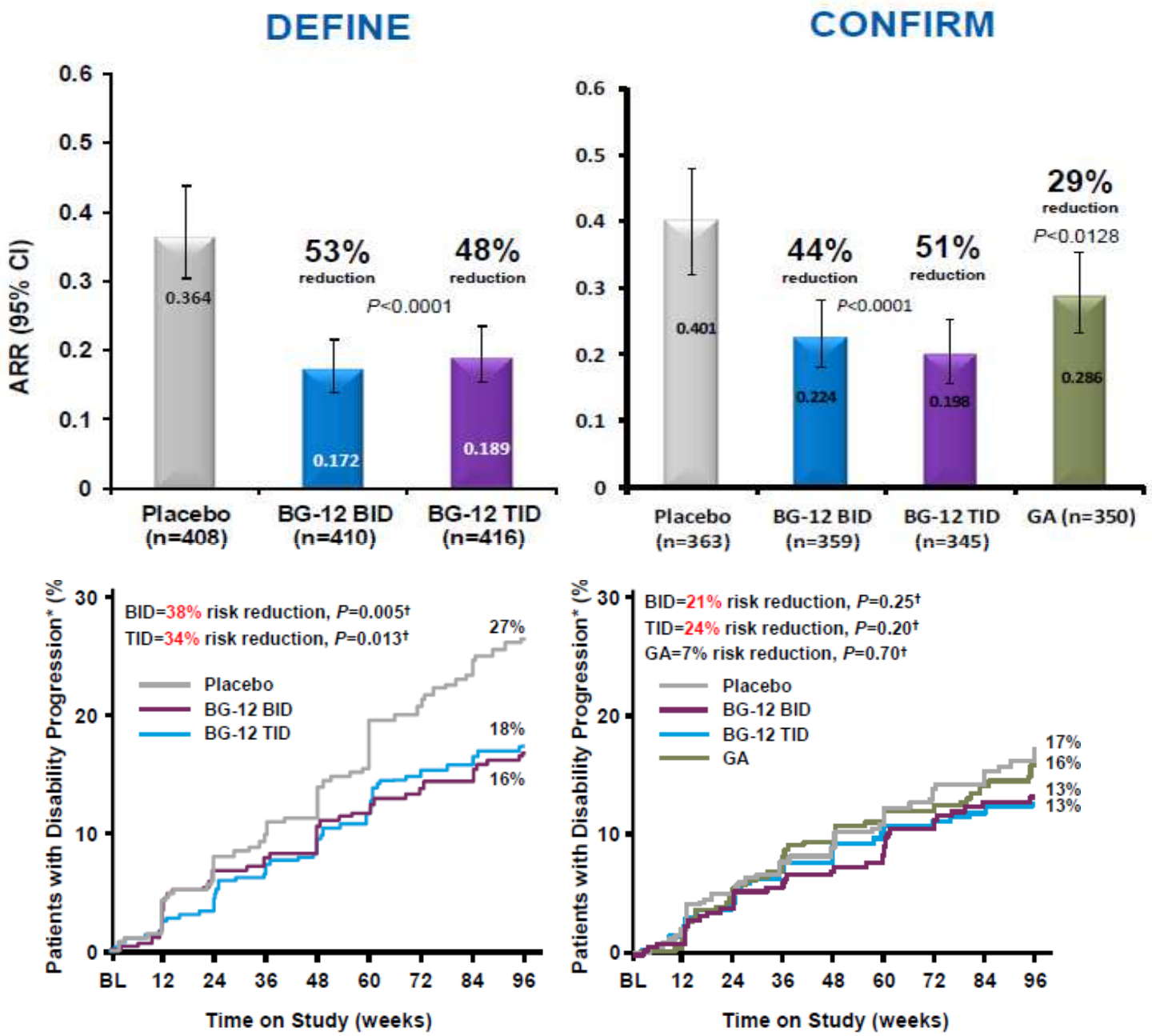
ESTABLISHED IN 1812 SEPTEMBER 20, 2012 VOL. 367 NO. 12

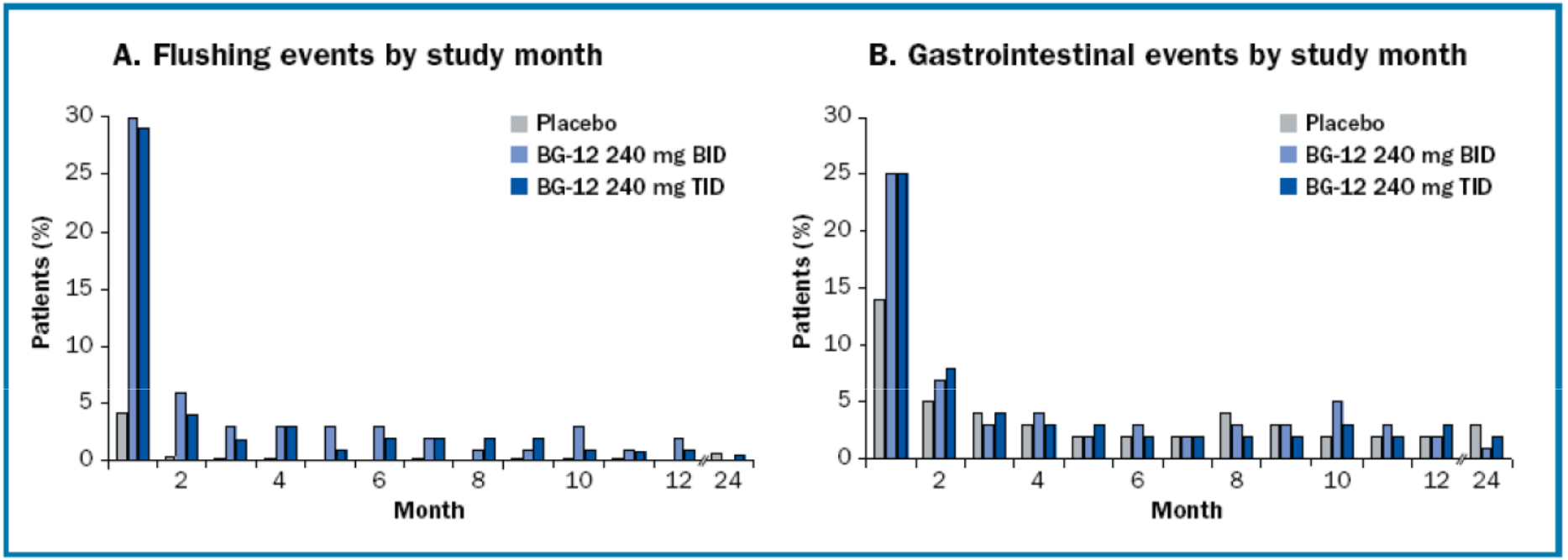
Placebo-Controlled Phase 3 Study of Oral BG-12 or Glatiramer in Multiple Sclerosis

Robert J. Fox, M.D., David H. Miller, M.D., J. Theodore Phillips, M.D., Ph.D., Michael Hutchinson, F.R.C.P., Eva Havrdova, M.D., Mariko Kita, M.D., Minhua Yang, M.S., Kartik Raghupathi, M.S., Mark Novas, M.D., Marianne T. Sweetser, M.D., Ph.D., Vissia Viglietta, M.D., Ph.D., and Katherine T. Dawson, M.D., for the CONFIRM Study Investigators*



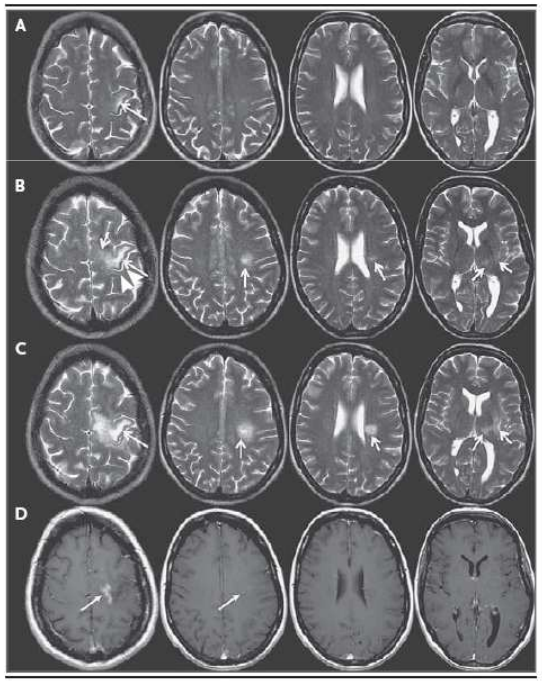



DEFINE
CONFIRM
ARR (95% CI)
0.6
0.5
0.4
0.3
0.2
0.1
0
0.364
0.172
0.189
53% reduction
48% reduction
P<0.0001
Placebo (n=408)
BG-12 BID (n=410)
BG-12 TID (n=416)
0.401
0.224
0.198
0.286
44% reduction
51% reduction
29% reduction
P<0.0128
P<0.0001
Placebo (n=363)
BG-12 BID (n=359)
BG-12 TID (n=345)
GA (n=350)
Patients with Disability Progression* (%
30
20
10
0
BID=38% risk reduction, P=0.005†
TID=34% risk reduction, P=0.013†
Placebo
BG-12 BID
BG-12 TID
27%
18%
16%
BL 12 24 36 48 60 72 84 96
Time on Study (weeks)
BID=21% risk reduction, P=0.25†
TID=24% risk reduction, P=0.20†
GA=7% risk reduction, P=0.70†
GA
17%
16%
13%
13%


A. Flushing events by study month
Placebo
BG-12 240 mg BID
BG-12 240 mg TID
Patients (%)
30
25
20
15
10
5
0
2
4
6
8
10
12
24
Month
B. Gastrointestinal events by study month
Placebo
BG-12 240 mg BID
BG-12 240 mg TID
Patients (%)
30
25
20
15
10
5
0
2
4
6
8
10
12
24
Month

PML in a Patient Treated with Dimethyl Fumarate from a Compounding Pharmacy

Bob W. van Oosten, M.D., Ph.D.
Joep Killestein, M.D., Ph.D.
Frederik Barkhof, M.D., Ph.D.
Chris H. Polman, M.D., Ph.D.
Mike P. Wattjes, M.D.



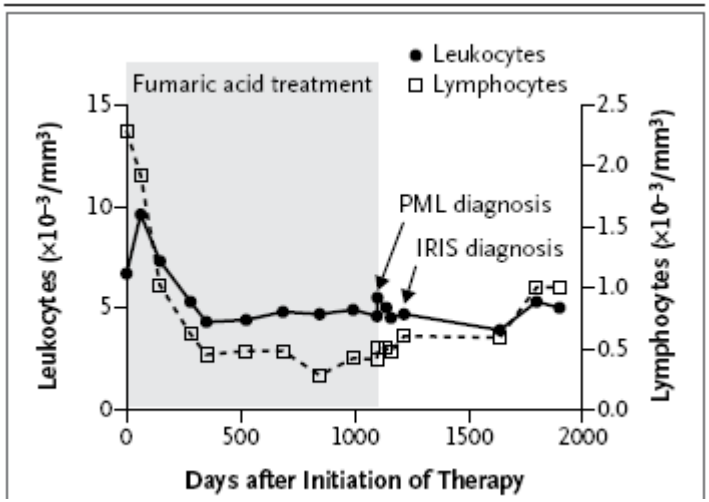
TO THE EDITOR: Preparations containing various mixtures of fumaric acid esters are prescribed for psoriasis in several countries, in many cases for off-label use, and are regarded as safe.[1] One such preparation is enteric-coated, slow-release Psorinovo (compounding pharmacy, Mierlo-Hout), in which the active agent is dimethyl fumarate and in which copper gluconate was used as an additive until 2010 (for a profile of the drug, see the Supplementary Appendix, available with the full text of this letter at NEJM.org).

On November 5, 2012, a 42-year-old woman who reported having progressive right-sided hemiparesis since May consulted us for a second opinion. She had been given a diagnosis of possible multiple sclerosis in September and at that time received 3000 mg of intravenous methylprednisolone over 3 days, without effect. Her medical history was notable for psoriasis, for which she had been taking 420 mg of Psorinovo per day since 2007, supplemented by 1000 mg of calcium ascorbate per day and EPA-1000 fish oil capsules (EPA denotes the omega-3 fatty acid eicosapentaenoic acid).

PML in a Patient Treated with Fumaric Acid

Ummehan Ermis
Joachim Weis, M.D.
Jörg B. Schulz, M.D.

We diagnosed progressive multifocal leukoencephalopathy (PML) in a 74-year-old man who had received monotherapy for psoriasis with oral fumaric acid for 3 years (2007 through 2010) in doses of up to 120 mg of dimethyl fumarate and 95 mg of monoethyl fumarate, each taken two times a day. The patient had had psoriasis for more than 5 years and had been treated topically with glucocorticoids (January through May 2005) and orally with acitretin (maximum dose of 50 mg once daily, May 2005 through June 2006) and methotrexate (maximum dose of 22.5 mg once weekly, July 2006 through July 2007). In July 2010, progressive sensory aphasia developed. Magnetic resonance imaging (MRI) of the brain (see Fig. S1



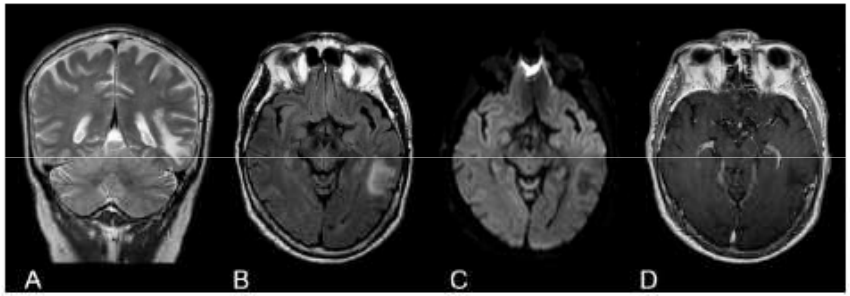
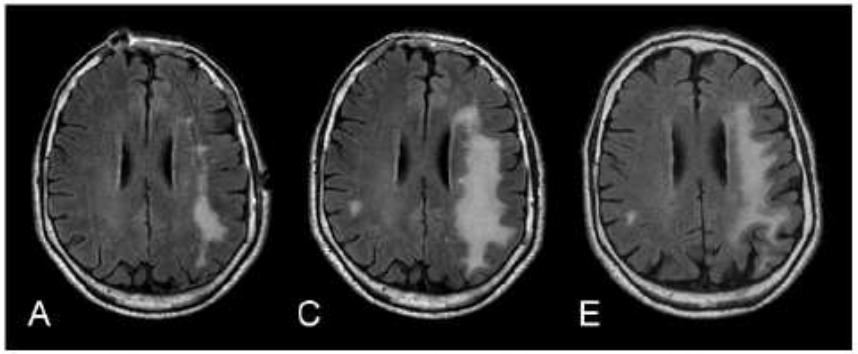


Figure S1: MR imaging at the time of presentation.

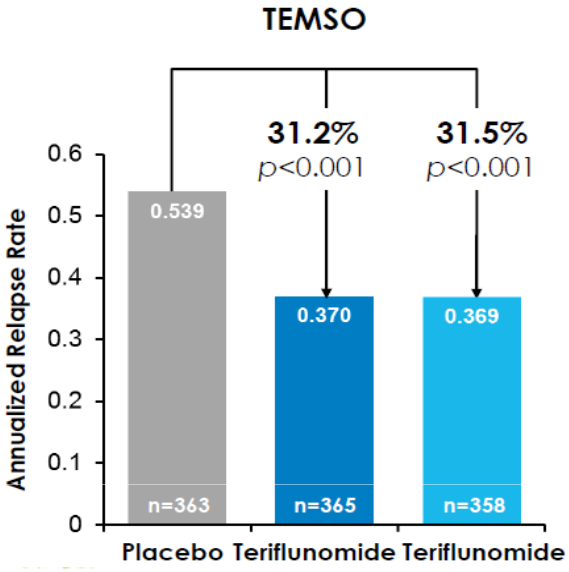


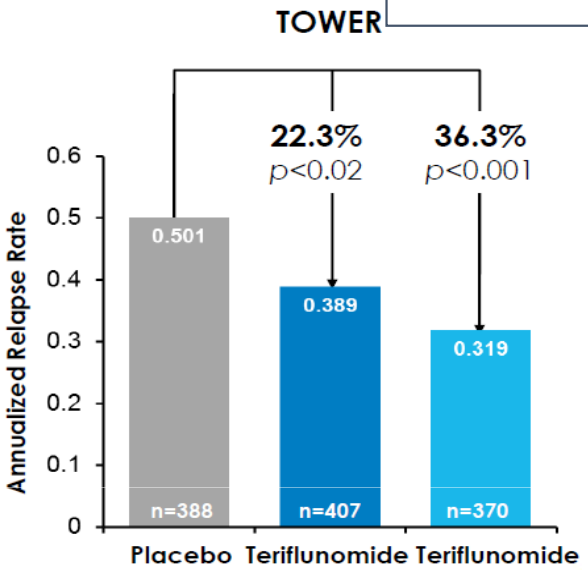
MR imaging characteristics of IRIS.

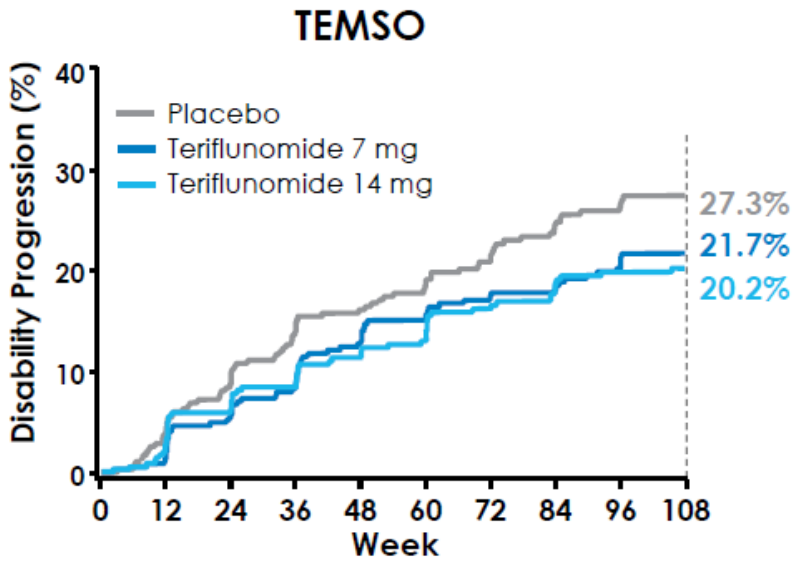
Teriflunomide

Randomized Trial of Oral Teriflunomide for Relapsing Multiple Sclerosis

Paul O'Connor, M.D., Jerry S. Wolinsky, M.D., Christian Confavreux, M.D., Giancarlo Comi, M.D., Ludwig Kappos, M.D., Tomas P. Olsson, M.D., Ph.D., Hadj Benzerdjeb, M.D., Philippe Truffinet, M.D., Lin Wang, Ph.D., Aaron Miller, M.D., and Mark S. Freedman, M.D., for the TEMSO Trial Group*







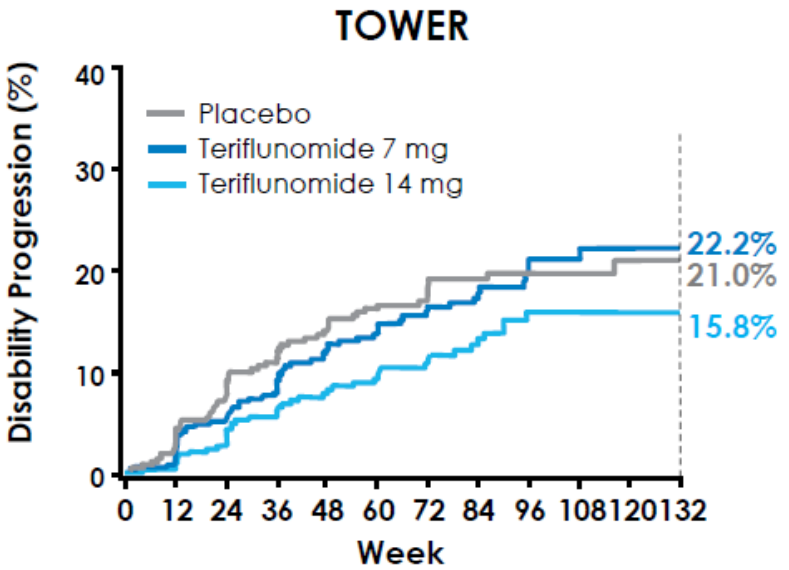
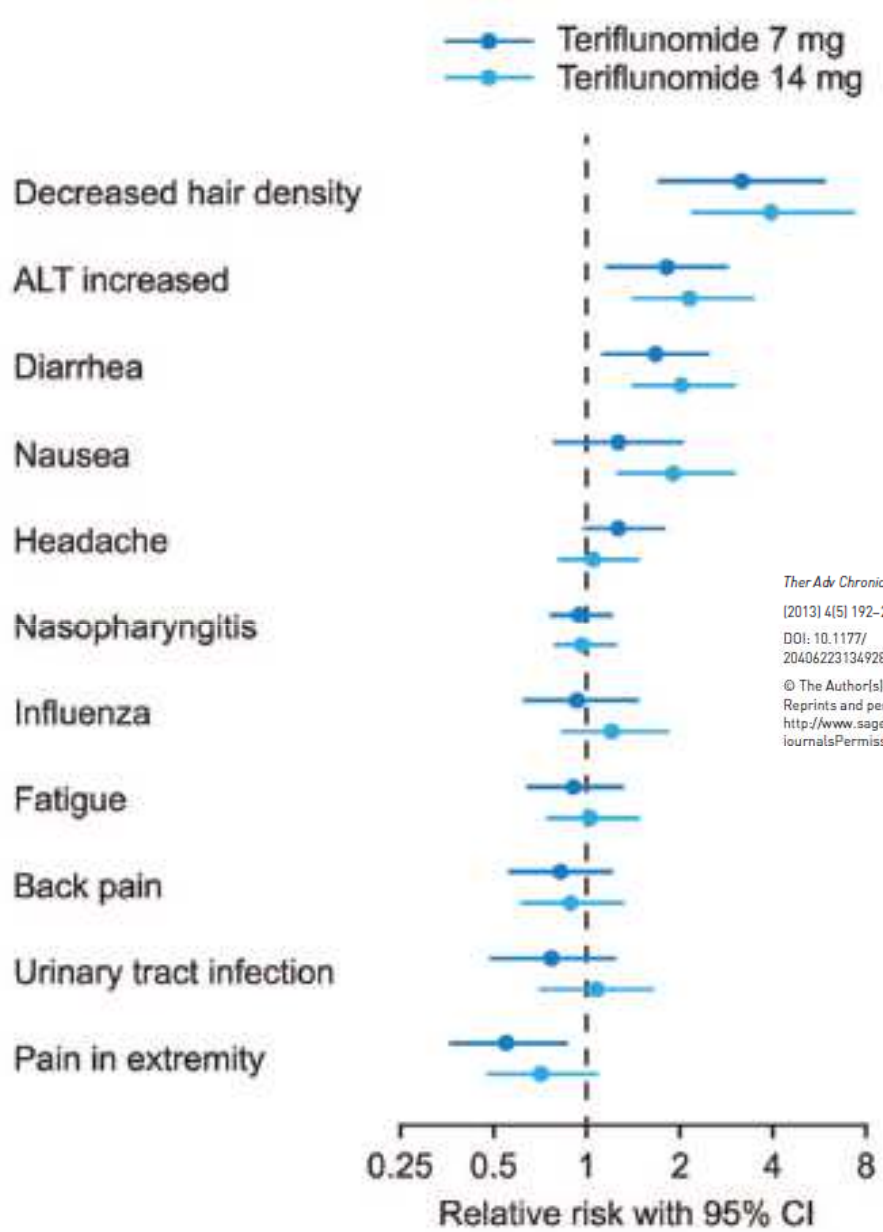


Table 3. Adverse Events.*

Adverse Event	Placebo (N = 360)	Teriflunomide, 7 mg (N = 368)	Teriflunomide, 14 mg (N = 358)
	number of patients (percent)		
All events			
At least one adverse event	315 (87.5)	328 (89.1)	325 (90.8)
Any adverse event leading to discontinuation of study medication	29 (8.1)	36 (9.8)	39 (10.9)
Any serious adverse event	46 (12.8)	52 (14.1)	57 (15.9)
Any event leading to death	0	0	0
Most common adverse events†			
Nasopharyngitis	98 (27.2)	94 (25.5)	93 (26.0)
Headache	64 (17.8)	81 (22.0)	67 (18.7)
Diarrhea	32 (8.9)	54 (14.7)	64 (17.9)
Fatigue	51 (14.2)	47 (12.8)	52 (14.5)
Elevated alanine aminotransferase level‡	24 (6.7)	44 (12.0)	51 (14.2)
Nausea	26 (7.2)	33 (9.0)	49 (13.7)
Hair thinning or decreased hair density	12 (3.3)	38 (10.3)	47 (13.1)
Influenza	36 (10.0)	34 (9.2)	43 (12.0)
Back pain	47 (13.1)	39 (10.6)	41 (11.5)
Urinary tract infection	35 (9.7)	27 (7.3)	37 (10.3)
Pain in arms or legs	47 (13.1)	26 (7.1)	33 (9.2)



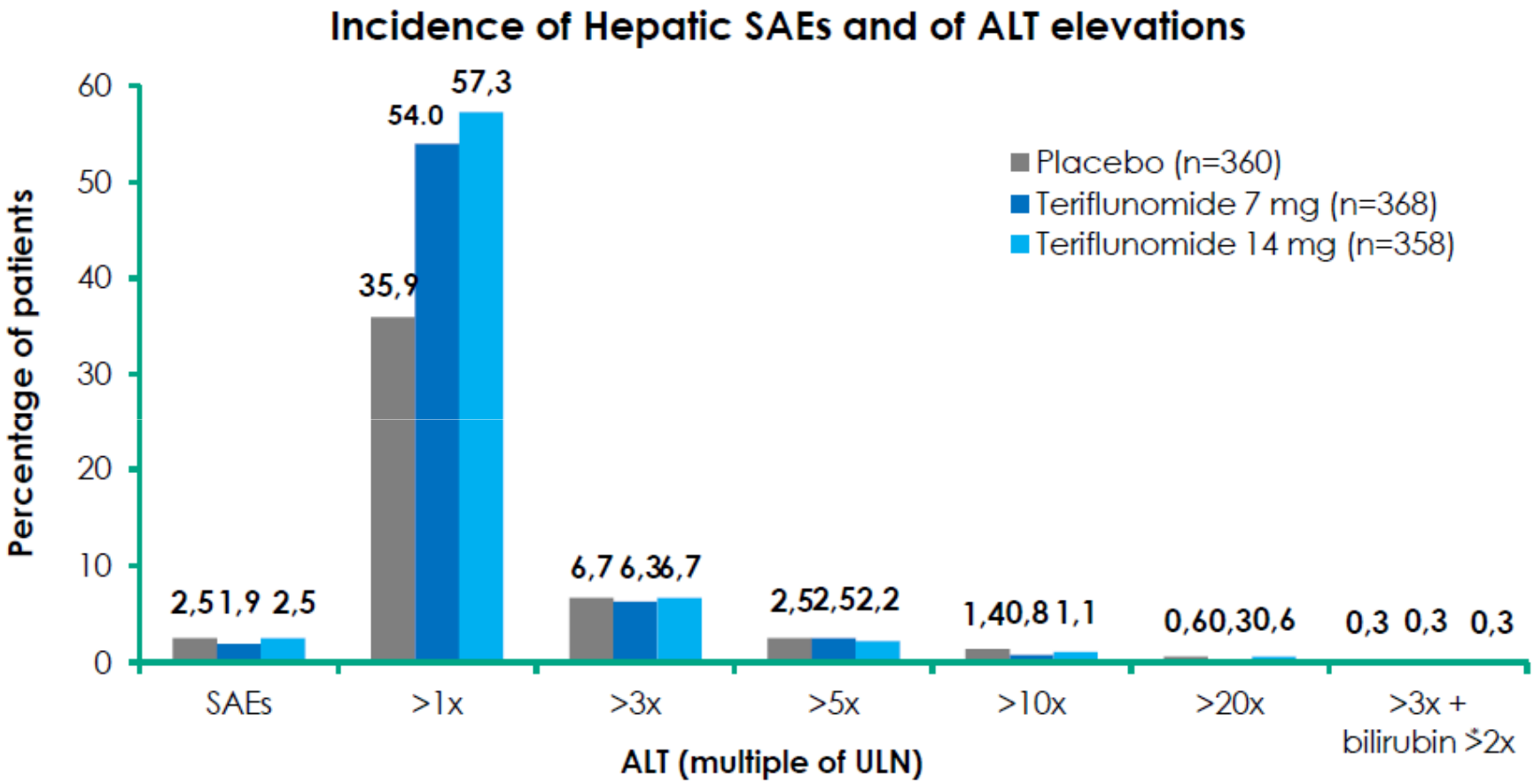
Ther Adv Chronic Dis

(2013) 4(5) 192–205

DOI: 10.1177/
2040622313492810

Teriflunomide in relapsing multiple sclerosis: therapeutic utility

Mark S. Freedman


Incidence of Hepatic SAEs and of ALT elevations
Percentage of patients
60
50
40
30
20
10
0
Placebo (n=360)
Teriflunomide 7 mg (n=368)
Teriflunomide 14 mg (n=358)
2,5
1,9
2,5
35,9
54.0
57,3
6,7
6,3
6,7
2,5
2,2
2,2
1,4
0,8
1,1
0,6
0,3
0,6
0,3
0,3
0,3
SAEs
>1x
>3x
>5x
>10x
>20x
>3x + bilirubin *2x
ALT (multiple of ULN)

AE – n (%)	TEMSO			TOWER		
	Placebo (n=360)	Teri 7 mg (n=368)	Teri 14 mg (n=358)	Placebo (n=385)	Teri 7 mg (n=409)	Teri 14 mg (n=371)
Infection	209 (58.1)	220 (59.8)	222 (62.0)	197 (51.2)	198 (48.4)	165 (44.5)
Bronchitis	22 (6.1)	18 (4.9)	29 (8.1)	20 (5.2)	19 (4.6)	11 (3.0)
Rinopharyngitis	98 (27.2)	94 (25.5)	93 (26.0)	68 (17.7)	49 (12.0)	44 (11.9)
Upper respiratory tract infection	25 (6.9)	34 (9.2)	32 (8.9)	44 (11.4)	37 (9.0)	34 (9.2)
Urinary tract infection	35 (9.7)	27 (7.3)	37 (10.3)	37 (9.6)	37 (9.0)	23 (6.2)
Influenza	36 (10.0)	34 (9.2)	43 (12.0)	21 (5.5)	21 (5.1)	23 (6.2)
Sinusitis	16 (4.4)	15 (14.1)	23 (6.4)	15 (3.9)	24 (5.9)	23 (6.2)

- 1 case of intestinal tuberculosis was reported in the teriflunomide 14 mg arm in TOWER
- 1 patient who developed tuberculosis went off study and was successfully treated (from pooled phase 2 and TEMSO analysis)
- 1 patient developed hepatitis with cytomegalovirus infection in the teriflunomide 14 mg arm in TEMSO

RICADUTE PRATICHE-ORGANIZZATIVE

Sorveglianza-monitoraggio della funzionalità epatica, ogni 2 settimane nei primi 6 mesi

Sorveglianza per rischio infezioni, selezione all'ingresso

- **Eventi avversi noti: implemetazione di strategie di risk management**

- **Eventi avversi rari di insorgenza non prevista/prevedibile: planning di programmi di sorveglianza**

FARMACI NUOVI

COME VALUTARE LA SAFETY E RAPPORTO RISCHI/BENEFICI

- **Trial clinici randomizzati controllati (RCTs) con placebo**
- **Estensione RCTs**
- **Trial clinici non randomizzati (in aperto, osservazionali)**
- **Studi di post-marketing**

COME VALUTARE LA SAFETY E RAPPORTO RISCHI/BENEFICI

- **Trial clinici randomizzati controllati (RCTs) con placebo**
- Estensione RCTs
- Trial clinici non randomizzati (in aperto, osservazionali)
- Studi di post-marketing

Phase III RCT

PROS

- Participants are good representatives for the target disease
- Good quality information on short-term incidence rate of ARs
- Appropriate follow-up
- Accurate lab tests
- Well specified indication(s)

DURATA

- Limitata durata del trial, impossibilità a riconoscere reazioni avverse tardive

DIMENSIONE

- Intorno a 1000 soggetti esposti, impossibilità a riconoscere eventi rari

RAPPRESENTATIVITA'

- Casistica selezionata (rigidi criteri di inclusione/esclusione
- Alcune categorie di soggetti escluse: popolazione pediatrica, anziana, donne in gravidanza/allattamento, casi con patologie associate, precedente esposizione a complessi trattamenti

COME VALUTARE LA SAFETY E RAPPORTO RISCHI/BENEFICI

- Trial clinici randomizzati controllati (RCTs) con placebo
- **Estensione RCTs**
- Trial clinici non randomizzati (in aperto, osservazionali)
- Studi di post-marketing

Studi di estensione dei trials clinici randomizzati con placebo

- dati aggiuntivi di efficacia
- dati aggiuntivi di safety

ma …

- assenza di cecità
- meno efficace standardizzazione delle procedure
- drop-outs,
- aderenza al trattamento/esposizione al farmaco meno valutabili

COME VALUTARE LA SAFETY E RAPPORTO RISCHI/BENEFICI

- Trial clinici randomizzati controllati (RCTs) con placebo
- Estensione RCTs
- **Trial clinici non randomizzati (in aperto, osservazionali)**
- **Studi di post-marketing**

Studi clinici randomizzati vs non randomizzati

RCT	NROT
• Verifica l'efficacia di un trattamento in gruppi selezionati di pazienti che potenzialmente potrebbero trarre il maggior beneficio dal trattamento	• Verifica l'efficacia di un trattamento in popolazioni eterogenee di pazienti che potrebbero trarre un potenziale beneficio dal trattamento
• Randomizzazione. Fattori di confondimento noti e non-noti possono essere corretti	• L'assegnazione del trattamento si basa sulla decisione del clinico. Fattori di confondimento noti possono essere corretti
• Placebo o altro farmaco attivo come gruppo di confronto	• Il gruppo di confronto è rappresentato da pazienti che assumono la terapia tradizionale
• Valutazione in cieco	• Valutazione in aperto
• Follow-up a breve termine	• Follow-up a lungo termine
• Regime di dosaggio inflessibile	• Regime di dosaggio inflessibile
• Misure di esito deboli o uso di "outcome surrogati"	• Misure di esito robuste
• Estremamente costoso	• Poco costoso

Studi osservazionali non randomizzati a lungo termine

Gli studi osservazionali non randomizzati (NROTs) includono un'ampia gamma di disegni di studio, come gli studi prospettici e retrospettivi di coorte, gli studi caso-controllo e quelli trasversali, con la caratteristica comune che qualunque intervento studiato è determinato dalla pratica clinica e non dal protocollo. I dati derivati dagli NROT possono essere particolarmente utili per valutare l'efficacia dei trattamenti in sottogruppi non studiati negli RCT, per rilevare effetti collaterali rari dei farmaci ed eventuali interazioni tra farmaci;

Trojano 2011

Gli studi di post-marketing – la farmacovigilanza

Problemi, limiti:

- Carenze nella segnalazione, rilevamento sottostimato
- Scarsa accuratezza del rilevamento/della descrizione
- Difficile stima dei soggetti esposti

Problemi correlati a SM

- Farmaci: più d'uno, in sequenza/ associazione
- Trattamenti concomitanti, sintomatici o per comorbilità
- comorbilità

Strumenti

- Segnalazione a autorità sanitarie
- Registri farmaco
- Registri malattia

Gli studi di post-marketing – la farmacovigilanza

Problemi, limiti:

- Carenze nella segnalazione, rilevamento sottostimato
- Scarsa accuratezza del rilevamento/della descrizione
- Difficile stima dei soggetti esposti

Problemi correlati a SM

- Farmaci: più d'uno, in sequenza/ associazione
- Trattamenti concomitanti, sintomatici o per comorbilità
- comorbilità

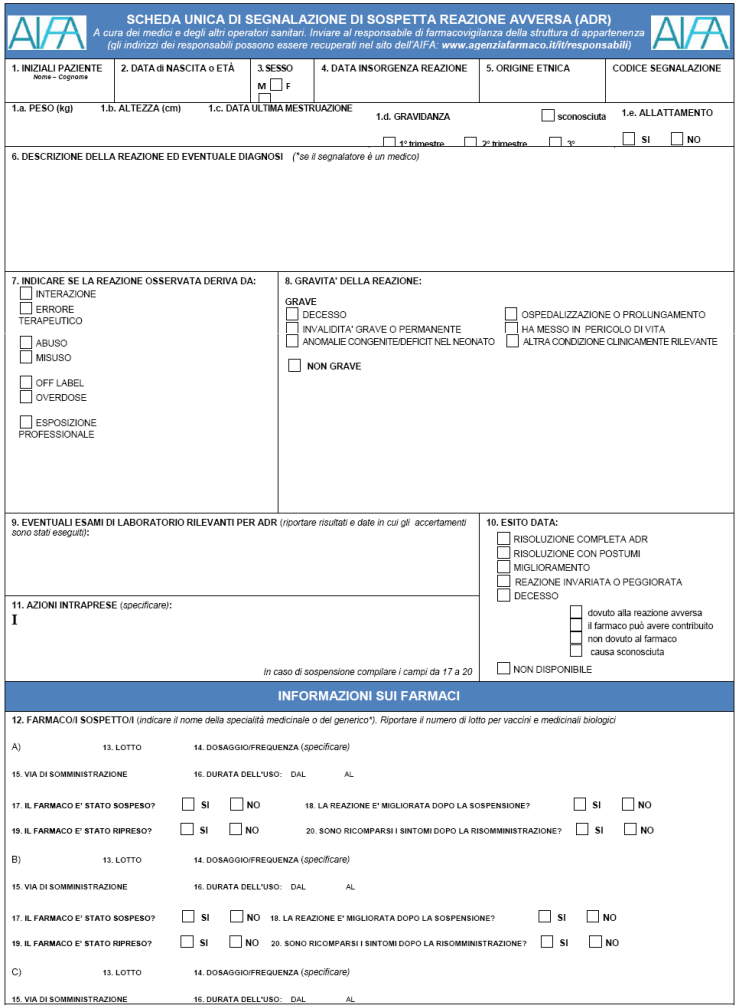
Strumenti

- Segnalazione a autorità sanitarie
- Registri farmaco
- Registri malattia

Gli studi di post-marketing – la farmacovigilanza

Strumenti

- AIFA - Segnalazione a autorità sanitarie
- Registri farmaco
- Registri malattia



SCHEDA UNICA DI SEGNALAZIONE DI SOSPETTA REAZIONE AVVERSA (ADR)

*A cura dei medici e degli altri operatori sanitari. Inviare al responsabile di farmacovigilanza della struttura di appartenenza (gli indirizzi dei responsabili possono essere recuperati nel sito dell'AIFA: **www.agenziafarmaco.it/it/responsabili**)*

1. INIZIALI PAZIENTE Nome – Cognome	2. DATA di NASCITA o ETÀ	3. SESSO M ☐ F ☐	4. DATA INSORGENZA REAZIONE	5. ORIGINE ETNICA	CODICE SEGNALAZIONE

1.a. PESO (kg) 1.b. ALTEZZA (cm) 1.c. DATA ULTIMA MESTRUAZIONE 1.d. GRAVIDANZA ☐ sconosciuta 1.e. ALLATTAMENTO

☐ 1° trimestre ☐ 2° trimestre ☐ 3° ☐ SI ☐ NO

6. DESCRIZIONE DELLA REAZIONE ED EVENTUALE DIAGNOSI *(*se il segnalatore è un medico)*

7. INDICARE SE LA REAZIONE OSSERVATA DERIVA DA:
- ☐ INTERAZIONE
- ☐ ERRORE TERAPEUTICO
- ☐ ABUSO
- ☐ MISUSO
- ☐ OFF LABEL
- ☐ OVERDOSE
- ☐ ESPOSIZIONE PROFESSIONALE

8. GRAVITA' DELLA REAZIONE:

GRAVE
- ☐ DECESSO
- ☐ INVALIDITA' GRAVE O PERMANENTE
- ☐ ANOMALIE CONGENITE/DEFICIT NEL NEONATO
- ☐ OSPEDALIZZAZIONE O PROLUNGAMENTO
- ☐ HA MESSO IN PERICOLO DI VITA
- ☐ ALTRA CONDIZIONE CLINICAMENTE RILEVANTE

☐ NON GRAVE

9. EVENTUALI ESAMI DI LABORATORIO RILEVANTI PER ADR *(riportare risultati e date in cui gli accertamenti sono stati eseguiti)*:

10. ESITO DATA:
- ☐ RISOLUZIONE COMPLETA ADR
- ☐ RISOLUZIONE CON POSTUMI
- ☐ MIGLIORAMENTO
- ☐ REAZIONE INVARIATA O PEGGIORATA
- ☐ DECESSO
  - ☐ dovuto alla reazione avversa
  - ☐ il farmaco può avere contribuito
  - ☐ non dovuto al farmaco
  - ☐ causa sconosciuta
- ☐ NON DISPONIBILE

11. AZIONI INTRAPRESE *(specificare)*:

In caso di sospensione compilare i campi da 17 a 20

INFORMAZIONI SUI FARMACI

12. FARMACO/I SOSPETTO/I *(indicare il nome della specialità medicinale o del generico*). Riportare il numero di lotto per vaccini e medicinali biologici*

A) 13. LOTTO 14. DOSAGGIO/FREQUENZA *(specificare)*

15. VIA DI SOMMINISTRAZIONE 16. DURATA DELL'USO: DAL AL

17. IL FARMACO E' STATO SOSPESO? ☐ SI ☐ NO 18. LA REAZIONE E' MIGLIORATA DOPO LA SOSPENSIONE? ☐ SI ☐ NO

19. IL FARMACO E' STATO RIPRESO? ☐ SI ☐ NO 20. SONO RICOMPARSI I SINTOMI DOPO LA RISOMMINISTRAZIONE? ☐ SI ☐ NO

B) 13. LOTTO 14. DOSAGGIO/FREQUENZA *(specificare)*

15. VIA DI SOMMINISTRAZIONE 16. DURATA DELL'USO: DAL AL

17. IL FARMACO E' STATO SOSPESO? ☐ SI ☐ NO 18. LA REAZIONE E' MIGLIORATA DOPO LA SOSPENSIONE? ☐ SI ☐ NO

19. IL FARMACO E' STATO RIPRESO? ☐ SI ☐ NO 20. SONO RICOMPARSI I SINTOMI DOPO LA RISOMMINISTRAZIONE? ☐ SI ☐ NO

C) 13. LOTTO 14. DOSAGGIO/FREQUENZA *(specificare)*

15. VIA DI SOMMINISTRAZIONE 16. DURATA DELL'USO: DAL AL

Il ruolo di EMA

The **Pharmacovigilance Risk Assessment Committee (PRAC)** is responsible for assessing all aspects of the risk management of medicines for human use.

This includes the ***detection, assessment, minimisation and communication*** relating to the risk of adverse reactions, while taking the therapeutic effect of the medicine into account. It also has responsibility for the design and evaluation of post-authorisation safety studies and pharmacovigilance audit.

The main responsibility of the PRAC is to prepare recommendations on any questions relating to pharmacovigilance activities related to a medicine for human use and on risk-management systems, including the monitoring of the effectiveness of those risk-management systems

European Medicines Agency

June 1995
CPMP/ICH/377/95

ICH Topic E 2 A
Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

Step 5

NOTE FOR GUIDANCE ON CLINICAL SAFETY DATA MANAGEMENT: DEFINITIONS AND STANDARDS FOR EXPEDITED REPORTING

(CPMP/ICH/377/95)

Gli studi di post-marketing – la farmacovigilanza

Strumenti

- Segnalazione a autorità sanitarie
- Registri farmaco
- Registri malattia

Neurol Sci (2008) 29:S235–S237
DOI 10.1007/s10072-008-0948-8

MULTIPLE SCLEROSIS: THE MANAGEMENT OF NON-RESPONDERS

Natalizumab: a country-based surveillance program

Gian Luigi Mancardi · Maria Pia Amato · Roberto D'Alessandro · Filippo Drago · Clara Milanese · Patrizia Popoli · Leandro Provinciali · Pasqualino Rossi · Giovanni Savettieri · Gioacchino Tedeschi · Maria Rosaria Tola · Nicola Vanacore · Anna Covezzoli · Marisa De Rosa · Carlo Piccinni · Nicola Montanaro · Laura Periotto · Antonio Addis · Nello Martini

NATALIZUMAB
Studi post-marketing per valutazione long-term di efficacia e sicurezza

	STRATA	TOUCH®	TYGRIS	TOP	Registro Gravidanze
Impegno con Autorità Regolatorie	●	●	●	●	●
Studio interventistico (IIIb)	●				
Obbligatorio per la prescrizione		●			
Programma osservazionale			●	●	●
Sicurezza: - Tutti i SAEs - Solo infezioni opport. - Status Ab anti-JCV	●	●	●	● ●	●
Efficacia (ricadute, EDSS)	●			●	
Numero di pazienti arruolabili: - controlli	~1.000	Illimitato	5.000	6.000 (●)	>300
Centri partecipanti	ROW	US	US+ROW	ROW	US+ROW
Durata (anni)	10	Illimitata	5	10	Illimitata

Gentilmente concessa da dott. Giannattasio, Biogen

I registri/studi osservazionali di fingolimod

PASS EU Post-Authorization Safety Study Pazienti 2a linea	PASS USA Post-Authorization Safety Study Pazienti 1a linea	Gilenya Pregnancy Registry	PANGAEA (Post-Authorization Non-interventional German sAfety of GilEnyA in RR MS patients)
Attivato in EU e in Usa per monitorare l'esposizione a lungo termine, fino a 5 anni, del trattamento con fingolimod. Previsto un arruolamento di circa 4000 pts fingolimod e 2000 in DMTs. L'esposizione totale ipotizzata sarà di 16.000 pazienti/anno		Lanciato in 10 nazioni. Sarà attivo per 6 anni e raccoglierà informazioni sull'esposizione a fingolimod in circa 500 gravidanze. Al 28 febbraio 2013, 15 gravidanze incluse.[1]	Attivato nel 2011 in Germania per stabilire la sicurezza e la tollerabilità di fingolimod nella pratica clinica e per indagarne gli aspetti farmacoeconomici. Il registro è aderente per struttura e contenuti all'RMP EMA. Al 31 luglio 2012 risultano arruolati 1819.[2]

Sono attivi molti registri su base nazionale o sub nazionale: «Pacific Northwest MS registry» ; «US Department of Defence Database» di cui non sono ancora disponbili i dati

[1]: Hellwig. Poster n. TBD ECTRIMS 2013; [2]: Ziemssen. Poster n. 522 ECTRIMS 2012

FINGOLIMOD, DATI DI POSTMARKETING

Aree di sorveglianza e di attenzione

1- Infezioni

- **Caso ulteriore di riattivazione erpetica**
- **Caso di PML**

2- Ambito cardiovascolare

- **Non ulteriori elementi di rilevanza in ambito cardiovascolare**

3- edema maculare

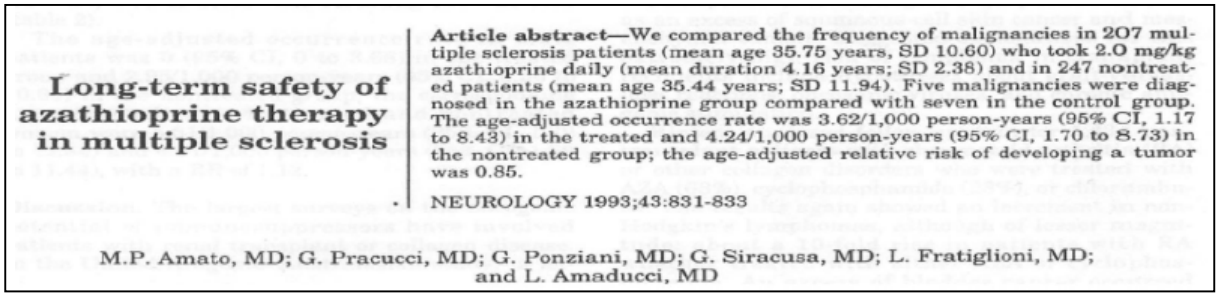
4- Altri eventi rari e imprevedibili: sindrome emofagocitaria

Gli studi di post-marketing – la farmacovigilanza

Strumenti

- Segnalazione a autorità sanitarie
- Registri farmaco
- Registri malattia

- **Dati demografici (sesso, età, fatt. geografici)**
- **Familiarità (SM, altre patologia)**
- **Storia dei trattamenti**
- **Comorbilità**
- **Dati clinici della SM**

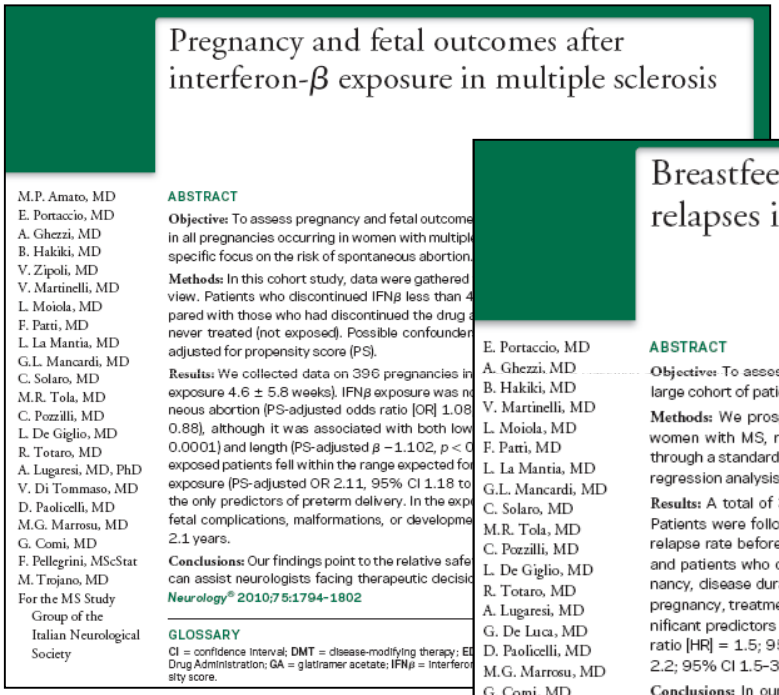


Long-term safety of azathioprine therapy in multiple sclerosis

Article abstract—We compared the frequency of malignancies in 207 multiple sclerosis patients (mean age 35.75 years, SD 10.60) who took 2.0 mg/kg azathioprine daily (mean duration 4.16 years; SD 2.38) and in 247 nontreated patients (mean age 35.44 years; SD 11.94). Five malignancies were diagnosed in the azathioprine group compared with seven in the control group. The age-adjusted occurrence rate was 3.62/1,000 person-years (95% CI, 1.17 to 8.43) in the treated and 4.24/1,000 person-years (95% CI, 1.70 to 8.73) in the nontreated group; the age-adjusted relative risk of developing a tumor was 0.85.

NEUROLOGY 1993;43:831-833

M.P. Amato, MD; G. Pracucci, MD; G. Ponziani, MD; G. Siracusa, MD; L. Fratiglioni, MD; and L. Amaducci, MD



Pregnancy and fetal outcomes after interferon-β exposure in multiple sclerosis

M.P. Amato, MD
E. Portaccio, MD
A. Ghezzi, MD
B. Hakiki, MD
V. Zipoli, MD
V. Martinelli, MD
L. Moiola, MD
F. Patti, MD
L. La Mantia, MD
G.L. Mancardi, MD
C. Solaro, MD
M.R. Tola, MD
C. Pozzilli, MD
L. De Giglio, MD
R. Totaro, MD
A. Lugaresi, MD, PhD
V. Di Tommaso, MD
D. Paolicelli, MD
M.G. Marrosu, MD
G. Comi, MD
F. Pellegrini, MScStat
M. Trojano, MD
For the MS Study Group of the Italian Neurological Society

ABSTRACT

Objective: To assess pregnancy and fetal outcome
in all pregnancies occurring in women with multipl
specific focus on the risk of spontaneous abortion.

Methods: In this cohort study, data were gathered
view. Patients who discontinued IFNβ less than 4
pared with those who had discontinued the drug
never treated (not exposed). Possible confounder
adjusted for propensity score (PS).

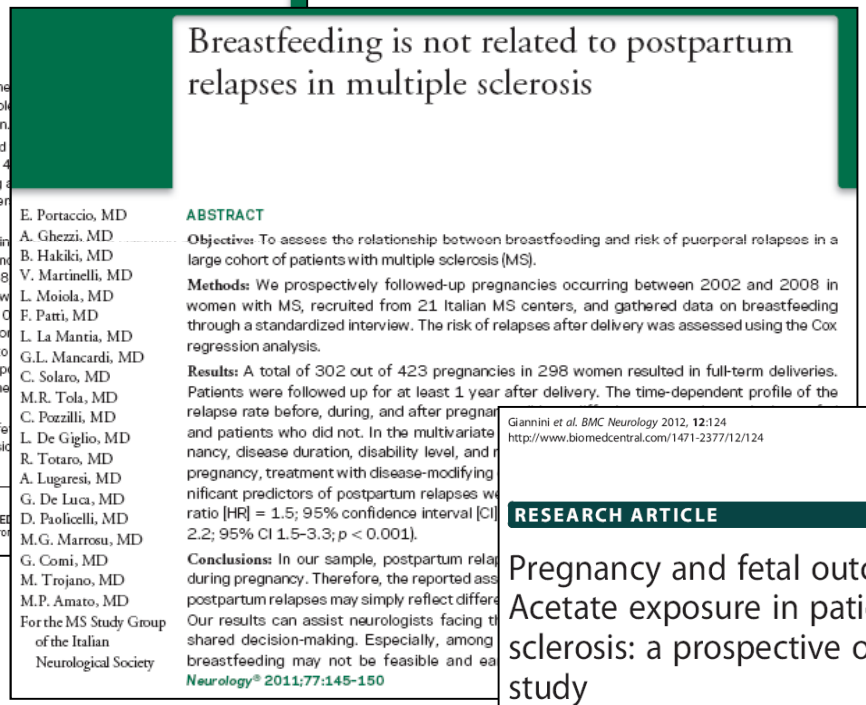
Results: We collected data on 396 pregnancies in
exposure 4.6 ± 5.8 weeks). IFNβ exposure was n
neous abortion (PS-adjusted odds ratio [OR] 1.08
0.88), although it was associated with both low
0.0001) and length (PS-adjusted β −1.102, $p <$ 0
exposed patients fell within the range expected fo
exposure (PS-adjusted OR 2.11, 95% CI 1.18 to
the only predictors of preterm delivery. In the exp
fetal complications, malformations, or developme
2.1 years.

Conclusions: Our findings point to the relative safe
can assist neurologists facing therapeutic decisio

Neurology® 2010;75:1794-1802

GLOSSARY

CI = confidence interval; DMT = disease-modifying therapy; ED
Drug Administration; GA = glatiramer acetate; IFNβ = interfero
sity score.



Breastfeeding is not related to postpartum relapses in multiple sclerosis

E. Portaccio, MD
A. Ghezzi, MD
B. Hakiki, MD
V. Martinelli, MD
L. Moiola, MD
F. Patti, MD
L. La Mantia, MD
G.L. Mancardi, MD
C. Solaro, MD
M.R. Tola, MD
C. Pozzilli, MD
L. De Giglio, MD
R. Totaro, MD
A. Lugaresi, MD
G. De Luca, MD
D. Paolicelli, MD
M.G. Marrosu, MD
G. Comi, MD
M. Trojano, MD
M.P. Amato, MD
For the MS Study Group of the Italian Neurological Society

ABSTRACT

Objective: To assess the relationship between breastfeeding and risk of puerperal relapses in a large cohort of patients with multiple sclerosis (MS).

Methods: We prospectively followed-up pregnancies occurring between 2002 and 2008 in women with MS, recruited from 21 Italian MS centers, and gathered data on breastfeeding through a standardized interview. The risk of relapses after delivery was assessed using the Cox regression analysis.

Results: A total of 302 out of 423 pregnancies in 298 women resulted in full-term deliveries. Patients were followed up for at least 1 year after delivery. The time-dependent profile of the relapse rate before, during, and after pregnan
and patients who did not. In the multivariate
nancy, disease duration, disability level, and
pregnancy, treatment with disease-modifying
nificant predictors of postpartum relapses w
ratio [HR] = 1.5; 95% confidence interval [CI]
2.2; 95% CI 1.5–3.3; $p < 0.001$).

Conclusions: In our sample, postpartum rela
during pregnancy. Therefore, the reported ass
postpartum relapses may simply reflect differ
Our results can assist neurologists facing t
shared decision-making. Especially, among
breastfeeding may not be feasible and ea

Neurology® 2011;77:145-150

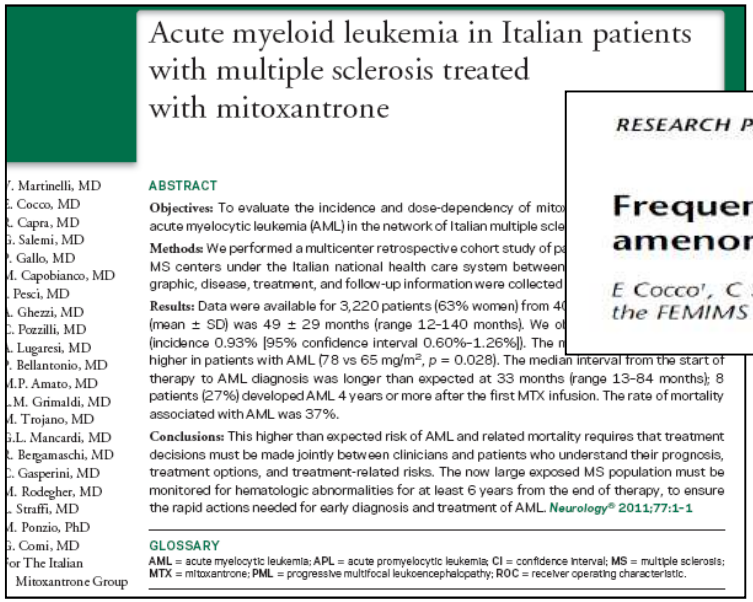
Giannini *et al. BMC Neurology* 2012, **12**:124
http://www.biomedcentral.com/1471-2377/12/124

BMC Neurology

RESEARCH ARTICLE Open Access

Pregnancy and fetal outcomes after Glatiramer Acetate exposure in patients with multiple sclerosis: a prospective observational multicentric study

Marta Giannini[1], Emilio Portaccio[1,14], Angelo Ghezzi[2], Bahia Hakiki[1,14], Luisa Pastò[1], Lorenzo Razzolini[1,14], Elisa Piscolla[1], Laura De Giglio[3], Carlo Pozzilli[3], Damiano Paolicelli[4], Maria Trojano[4], Maria Giovanna Marrosu[5], Francesco Patti[6], Loredana La Mantia[7], Gianluigi Mancardi[8], Claudio Solaro[9], Rocco Totaro[10], Maria Rosaria Tola[11], Giovanna De Luca[12], Alessandra Lugaresi[12], Lucia Moiola[13], Vittorio Martinelli[13], Giancarlo Comi[13] and Maria Pia Amato[1*]



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

V. Martinelli, MD
C. Cocco, MD
L. Capra, MD
G. Salemi, MD
P. Gallo, MD
M. Capobianco, MD
C. Pesci, MD
A. Ghezzi, MD
C. Pozzilli, MD
A. Lugaresi, MD
P. Bellantonio, MD
M.P. Amato, MD
L.M. Grimaldi, MD
M. Trojano, MD
G.L. Mancardi, MD
A. Bergamaschi, MD
C. Gasperini, MD
M. Rodegher, MD
L. Straffi, MD
M. Ponzio, PhD
G. Comi, MD
for The Italian Mitoxantrone Group

ABSTRACT

Objectives: To evaluate the incidence and dose-dependency of mitox
acute myelocytic leukemia (AML) in the network of Italian multiple scle

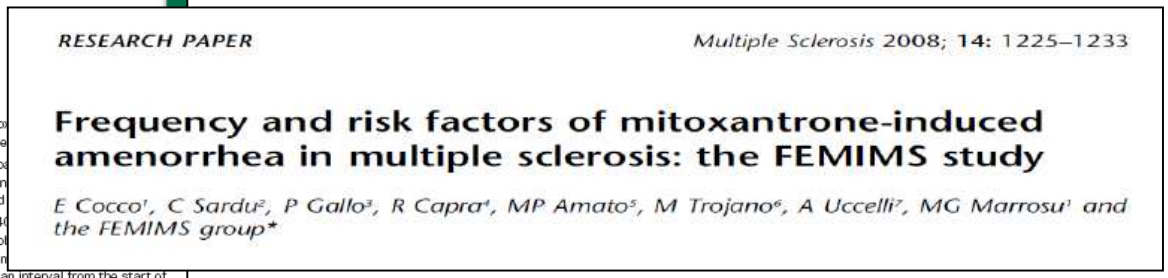
Methods: We performed a multicenter retrospective cohort study of pa
MS centers under the Italian national health care system between
graphic, disease, treatment, and follow-up information were collected

Results: Data were available for 3,220 patients (63% women) from 40
(mean ± SD) was 49 ± 29 months (range 12–140 months). We ob
(incidence 0.93% [95% confidence interval 0.60%–1.26%]). The m
higher in patients with AML (78 vs 65 mg/m², $p = 0.028$). The median interval from the start of therapy to AML diagnosis was longer than expected at 33 months (range 13–84 months); 8 patients (27%) developed AML 4 years or more after the first MTX infusion. The rate of mortality associated with AML was 37%.

Conclusions: This higher than expected risk of AML and related mortality requires that treatment decisions must be made jointly between clinicians and patients who understand their prognosis, treatment options, and treatment-related risks. The now large exposed MS population must be monitored for hematologic abnormalities for at least 6 years from the end of therapy, to ensure the rapid actions needed for early diagnosis and treatment of AML. *Neurology*® 2011;77:1-1

GLOSSARY

AML = acute myelocytic leukemia; **APL** = acute promyelocytic leukemia; **CI** = confidence interval; **MS** = multiple sclerosis; **MTX** = mitoxantrone; **PML** = progressive multifocal leukoencephalopathy; **ROC** = receiver operating characteristic.

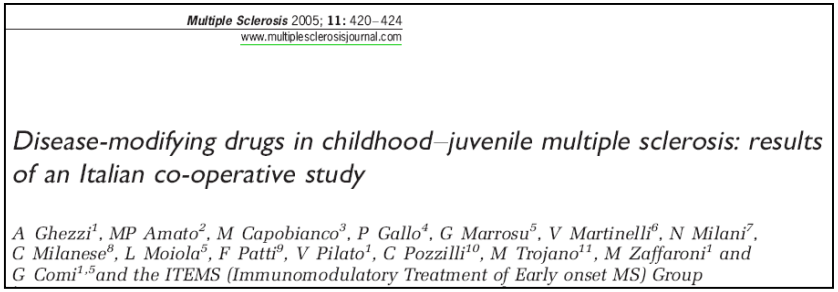


RESEARCH PAPER

Multiple Sclerosis 2008; **14:** 1225–1233

Frequency and risk factors of mitoxantrone-induced amenorrhea in multiple sclerosis: the FEMIMS study

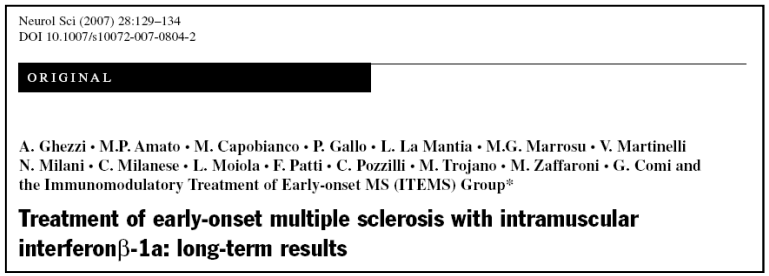
*E Cocco[1], C Sardu[2], P Gallo[3], R Capra[4], MP Amato[5], M Trojano[6], A Uccelli[7], MG Marrosu[1] and the FEMIMS group**



Multiple Sclerosis 2005; **11:** 420–424
www.multiplesclerosisjournal.com

Disease-modifying drugs in childhood–juvenile multiple sclerosis: results of an Italian co-operative study

A Ghezzi[1], MP Amato[2], M Capobianco[3], P Gallo[4], G Marrosu[5], V Martinelli[6], N Milani[7], C Milanese[8], L Moiola[5], F Patti[9], V Pilato[1], C Pozzilli[10], M Trojano[11], M Zaffaroni[1] and G Comi[1,5] and the ITEMS (Immunomodulatory Treatment of Early onset MS) Group

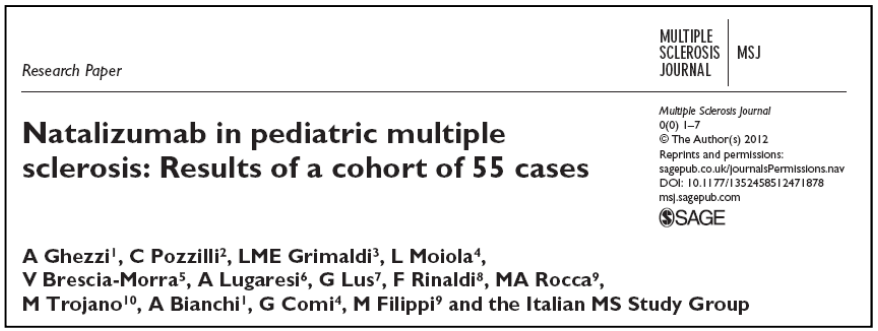


Neurol Sci (2007) 28:129–134
DOI 10.1007/s10072-007-0804-2

ORIGINAL

A. Ghezzi • M.P. Amato • M. Capobianco • P. Gallo • L. La Mantia • M.G. Marrosu • V. Martinelli N. Milani • C. Milanese • L. Moiola • F. Patti • C. Pozzilli • M. Trojano • M. Zaffaroni • G. Comi and the Immunomodulatory Treatment of Early-onset MS (ITEMS) Group*

Treatment of early-onset multiple sclerosis with intramuscular interferonβ-1a: long-term results



Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

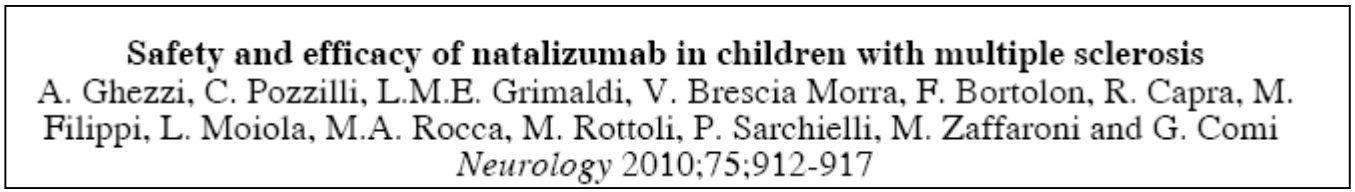
Multiple Sclerosis Journal
0(0) 1–7

DOI: 10.1177/1352458512471878
msj.sagepub.com

SAGE

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

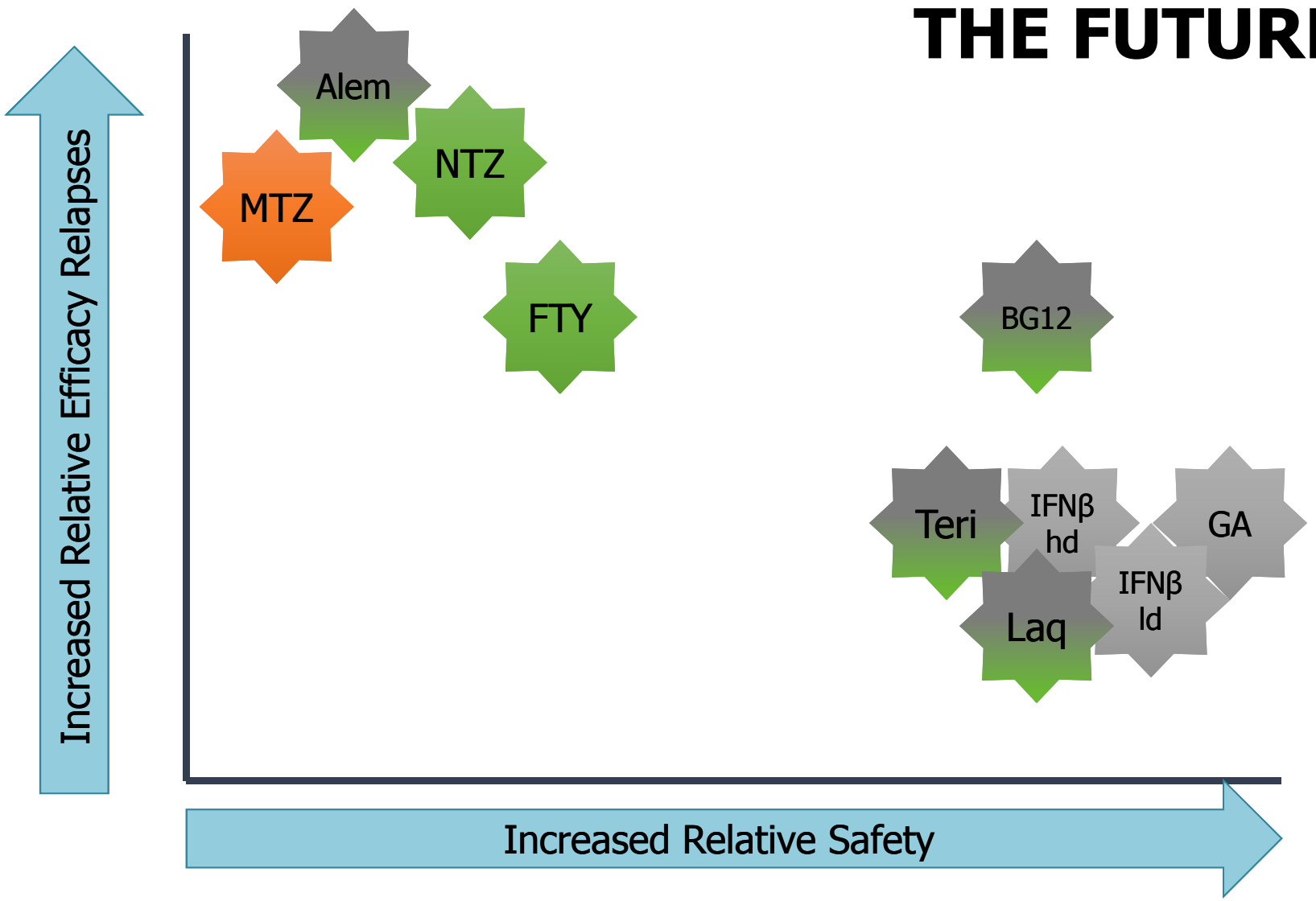


Safety and efficacy of natalizumab in children with multiple sclerosis

A. Ghezzi, C. Pozzilli, L.M.E. Grimaldi, V. Brescia Morra, F. Bortolon, R. Capra, M. Filippi, L. Moiola, M.A. Rocca, M. Rottoli, P. Sarchielli, M. Zaffaroni and G. Comi

Neurology 2010;75;912-917

Risk/Efficacy: Current Disease Modifying Drugs



da Montalban, 2013 modificata

Accurata conoscenza eventi avversi, strategie di prevenzione, monitoraggio, diagnosi precoce, trattamento adeguato (es. PML in Tysabri)

Eventi avversi rari: non riscontrabili in trials clinici
Trials clinici: popolazioni selezionate, minori comorbilità

⇒ Necessità di sorveglianza post-marketing

registri di farmaco?

registri di malattia?

Vantaggi dei registri di malattia

- dati demografici e clinici
- Storia dei precedenti trattamenti farmacologici (es. immunosoppressori)
- familiarità per patologie
- comorbilità

Necessità di azione congiunta
- Agenzie regolatorie
- società scientifiche
- centri clinici ⇒ organizzazione e strumenti organizzativi

GRAZIE PER L’ATTENZIONE