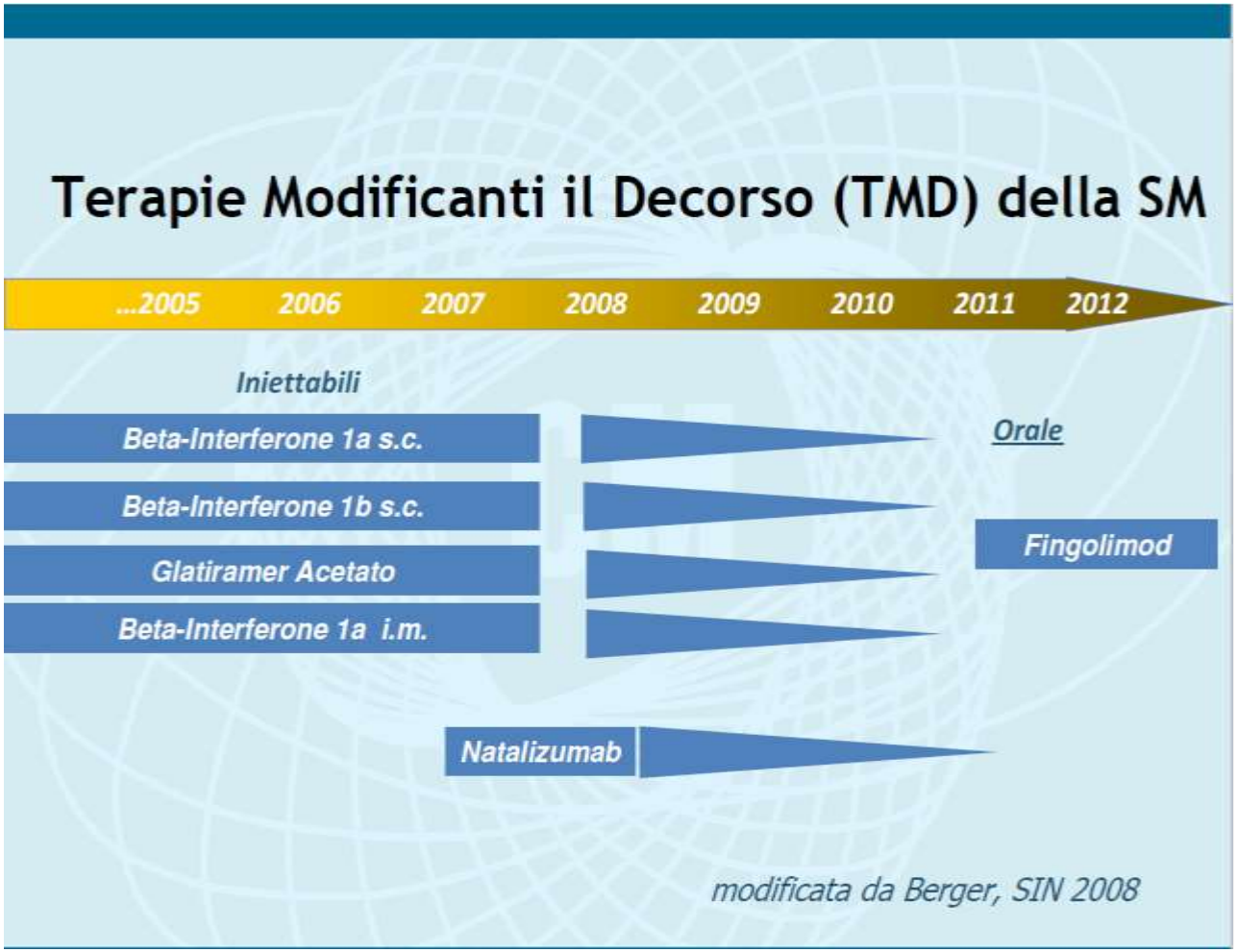
Cuore e cervello: rischi e potenzialità della terapia

Dott. ER Cosentino

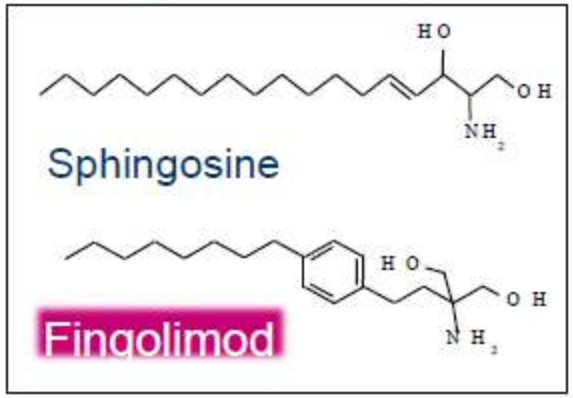
Dipartimento Cardio-Toraco-Vascolare

Università degli Studi di Bologna

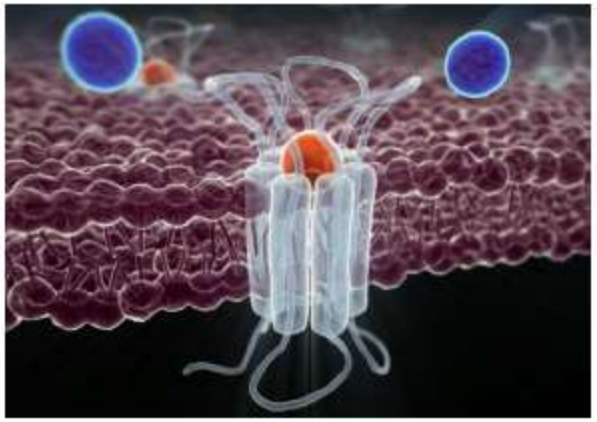
Evoluzione della terapia



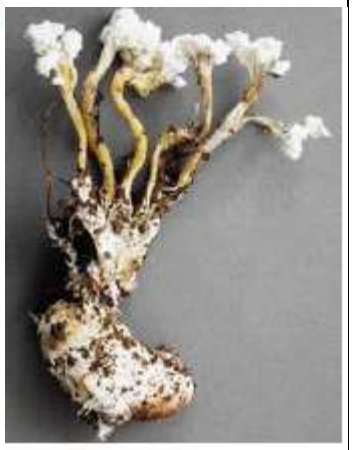
Fingolimod è un analogo strutturale della sfingosina



La sua struttura chimica è molto simile a quella della **sfingosina**, uno sfingolipide naturale delle cellule di mammifero che viene fosforilato all'interno della cellula e che agisce



- tramite specifici recettori accoppiati alla proteina G (**recettori S1P**).



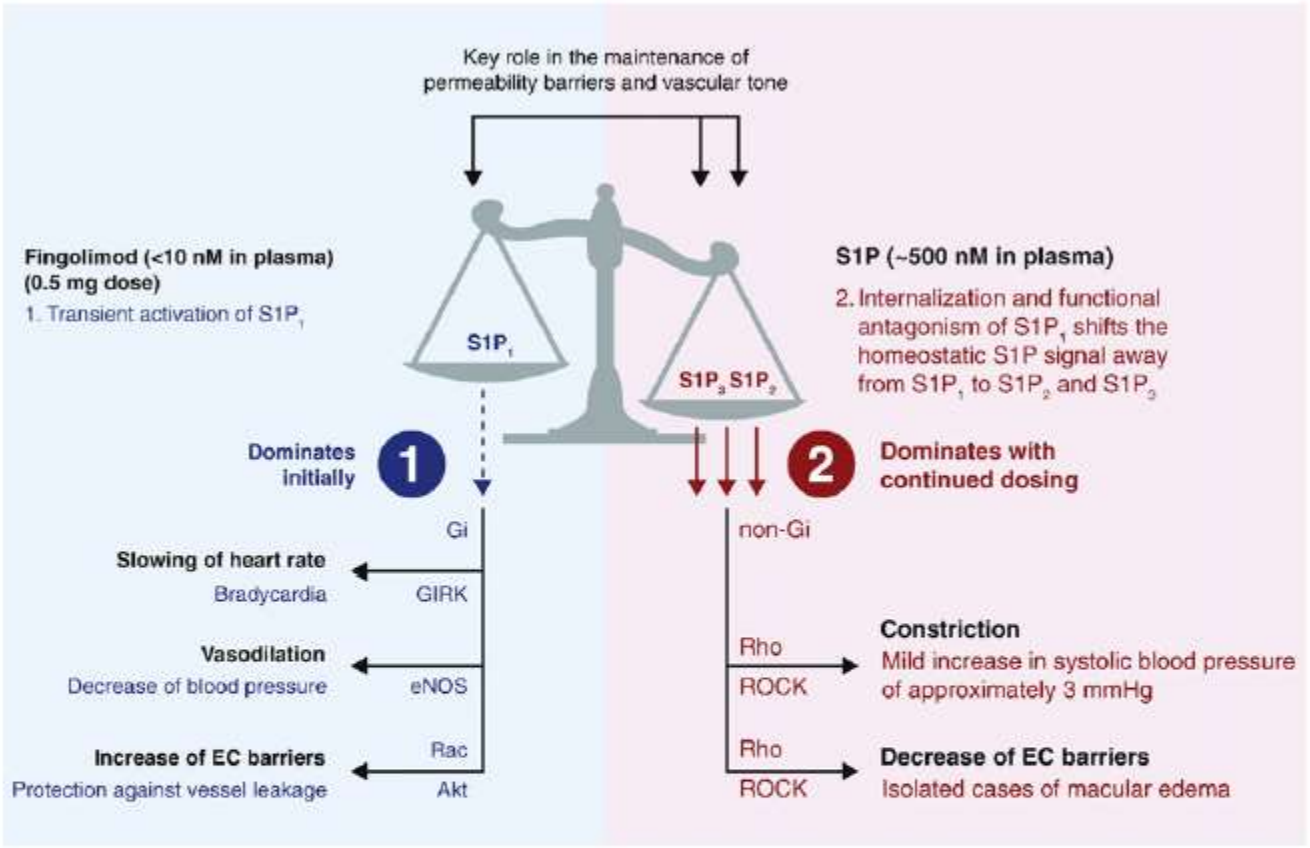
I recettori S1P sono espressi sia sui linfociti sia sulle cellule nervose

- Esistono 5 sottotipi di recettori S1P e sono coinvolti nella regolazione di diversi processi biologici;
- Fingolimod interagisce con 4 dei 5 sottotipi di recettori S1P (non lega S1P2).

Recettore *(la grandezza del carattere indica la rilevanza dell'azione di fingolimod)*	**Affinità di legame di Fingolimod-P** (nM)	**Distribuzione** (mRNA)	**Funzioni chiave mediate**
$S1P_1$	0.3	**Linfociti** **Cellule nervose** ECs, SMCs Miociti atriali	• **Fuoriuscita dei linfociti dai linfonodi** • **Migrazione/funzione astrociti** • **Modulazione di processi** • Tono vasomotorio, barriere endoteliali • Battito cardiaco
$S1P_2$	>10,000	ECs, SMCs	• Tono vasomotorio, barriere endoteliali
$S1P_3$	3.0	**Cellule nervose** ECs, SMCs Miociti atriali	• **Migrazione/funzione astrociti** • Tono vasomotorio, barriere endoteliali • Battito cardiaco
$S1P_4$	0.3	Linfociti (molto bassa)	Sconosciute
$S1P_5$	0.3	**Oligodendrociti**	• **Modulazione di processi**

Brinkmann, *Pharm & Ther* 2007

Figure 1



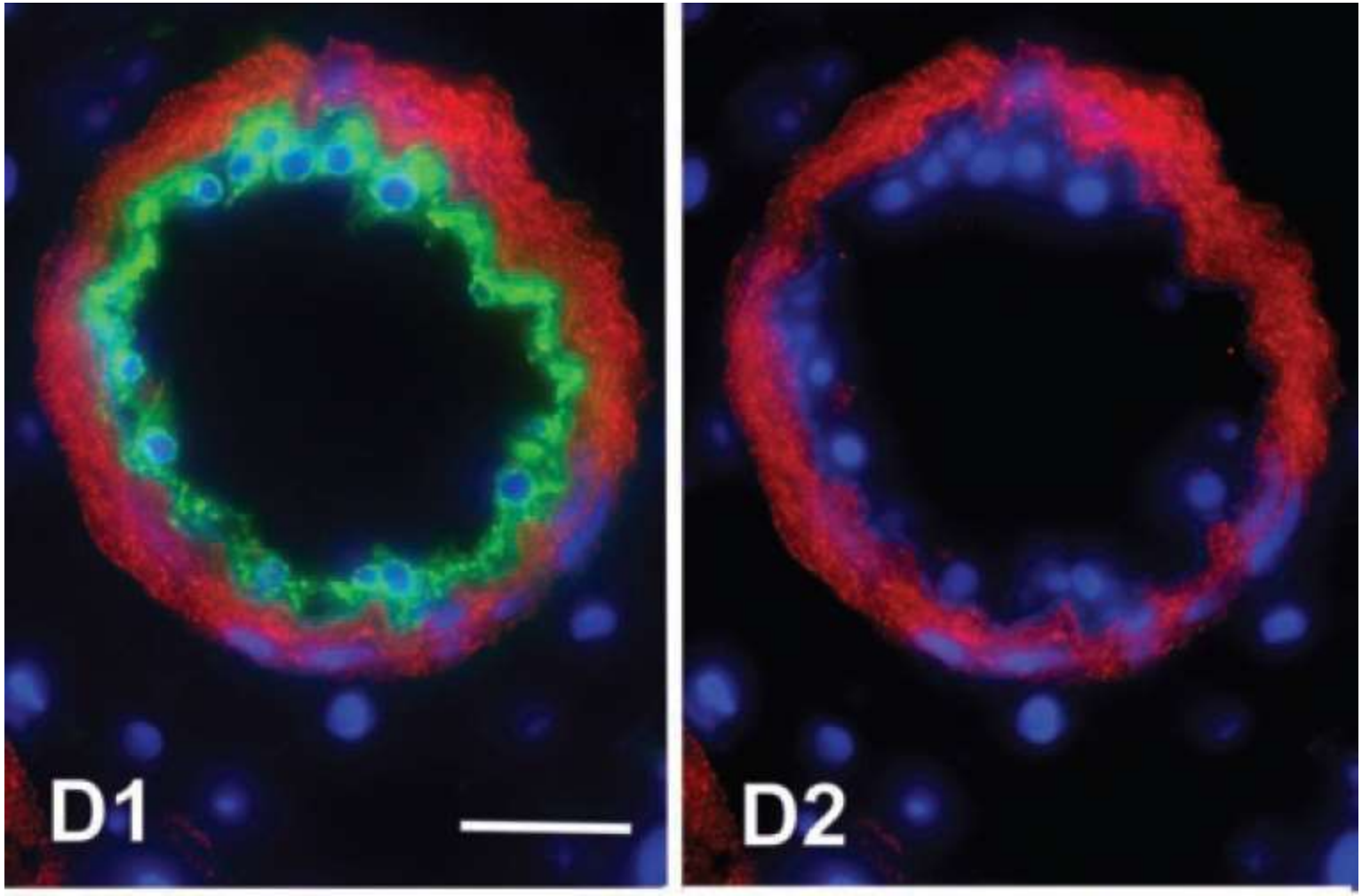
Shift in the balance of S1P signaling in response to fingolimod.[20,33,43-49] A high concentration of S1P (200-900 nM) is present in plasma and binds to $S1P_{1-3}$ suggesting that, in vivo, all vascular receptors are activated by the endogenous ligand responsible for controlling vascular tone and permeability. Initiating fingolimod therapy transiently activates $S1P_1$, resulting in activation of GIRK channels on atrial myocytes and, consequently, bradycardia; activation of eNOS and, subsequently, a decrease in blood pressure; and an increase in EC barriers protecting against vessel leakage. After this initial agonism, continuous dosing with fingolimod results in functional antagonism and down-regulation of $S1P_1$. Down-regulation of $S1P_1$ leads to enhanced activation of $S1P_2$ and $S1P_3$ by plasma S1P. This preferential signaling may increase activation of ROCK in VSMCs, which could lead to vasoconstriction and a decrease in EC barriers causing a mild increase in blood pressure and isolated cases of macular edema. *EC*, endothelial cell; *eNOS*, endothelial nitric oxide synthase; *fingolimod-P*, fingolimod phosphate; *Gi*, inhibitory G-protein subunit; *GIRK*, G-protein-coupled inwardly rectifying potassium; *ROCK*, Rho-kinase; *S1P*, sphingosine-1-phosphate; *$S1P_{1-3}$*, sphingosine-1-phosphate receptor subtypes 1–3.

Clinical Pharmacology

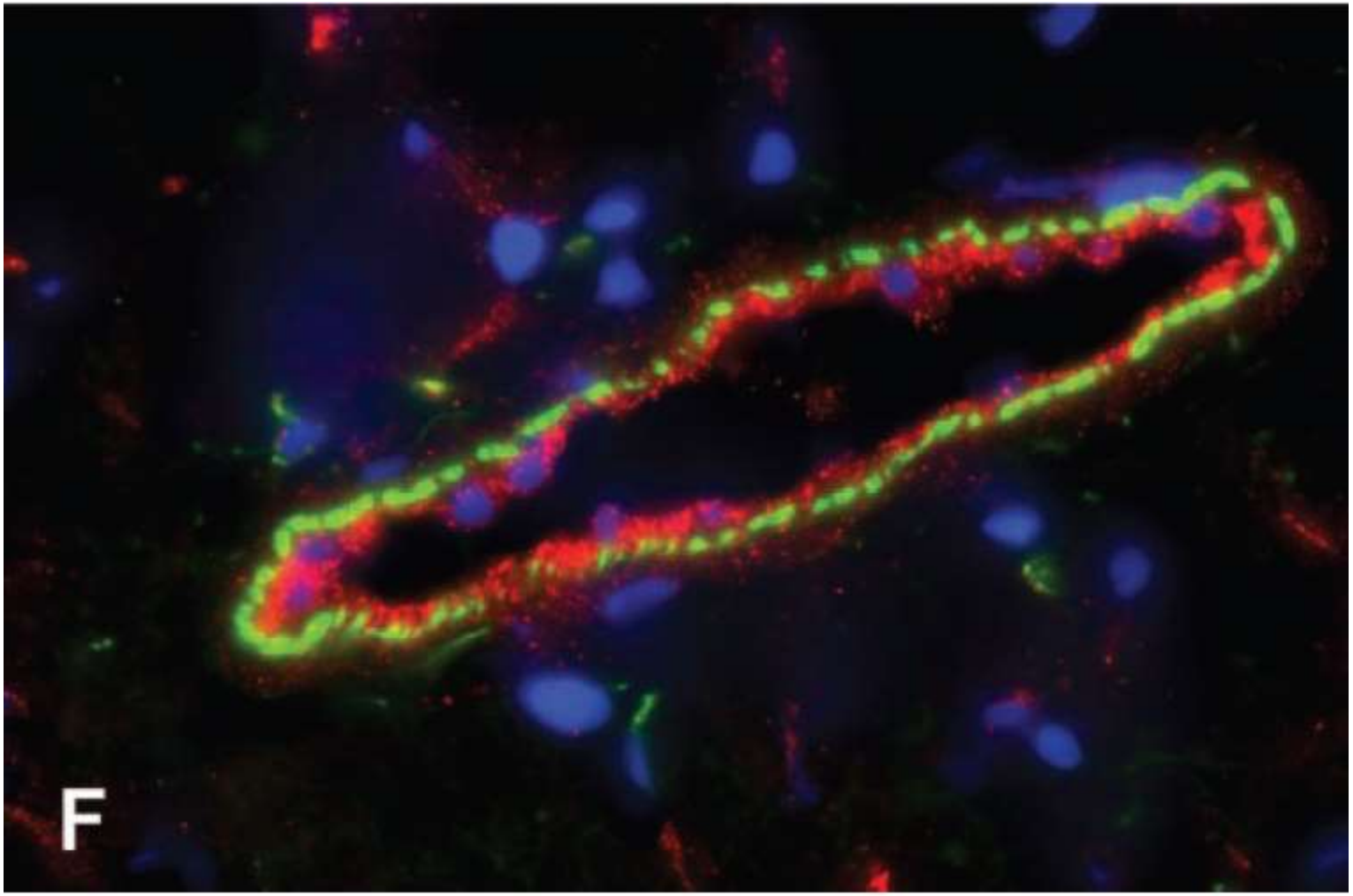
- >800 pts in Pharmacology studies using 0,5 to 40 mg dose
- High oral bioavailability with no food effect
- Metabolized by cytochrome CyP450-4F2; no DDI; no toxic metabolites
- T1/2 of 6-9 days
- No dose adjustment (renal, hepatic dysfunction, age, gender, race)

Pharmacodynamics

- Reduced lymphocyte count: 70% reduction at 0.5 mg steady state
- Heart rate decrease on day 1, attenuates over time
- Mild-moderate decrease in FEV1 at high dose (5.0 mg)



Forrest M et al, J Pharm Exp Ther 2004



Forrest M et al, J Pharm Exp Ther 2004

Unique Efficacy Profile in Relapsing MS

- Highly effective compared to placebo
- Strong efficacy compared to IFN beta-1a
- Doses of 0.5 mg and 1.25 mg per day studied in Phase 3 with similar results in both groups
- Efficacy on multiple, validated measures in large, well-controlled studies

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 4, 2010 VOL. 362 NO. 5

A Placebo-Controlled Trial of Oral Fingolimod in Relapsing Multiple Sclerosis

Ludwig Kappos, M.D., Ernst-Wilhelm Radue, M.D., Paul O'Connor, M.D., Chris Polman, M.D., Reinhard Hohlfeld, M.D., Peter Calabresi, M.D., Krzysztof Selmaj, M.D., Catherine Agoropoulou, Ph.D., Malgorzata Leyk, Ph.D., Lixin Zhang-Auberson, M.D., Ph.D., and Pascale Burtin, M.D., Ph.D., for the FREEDOMS Study Group*

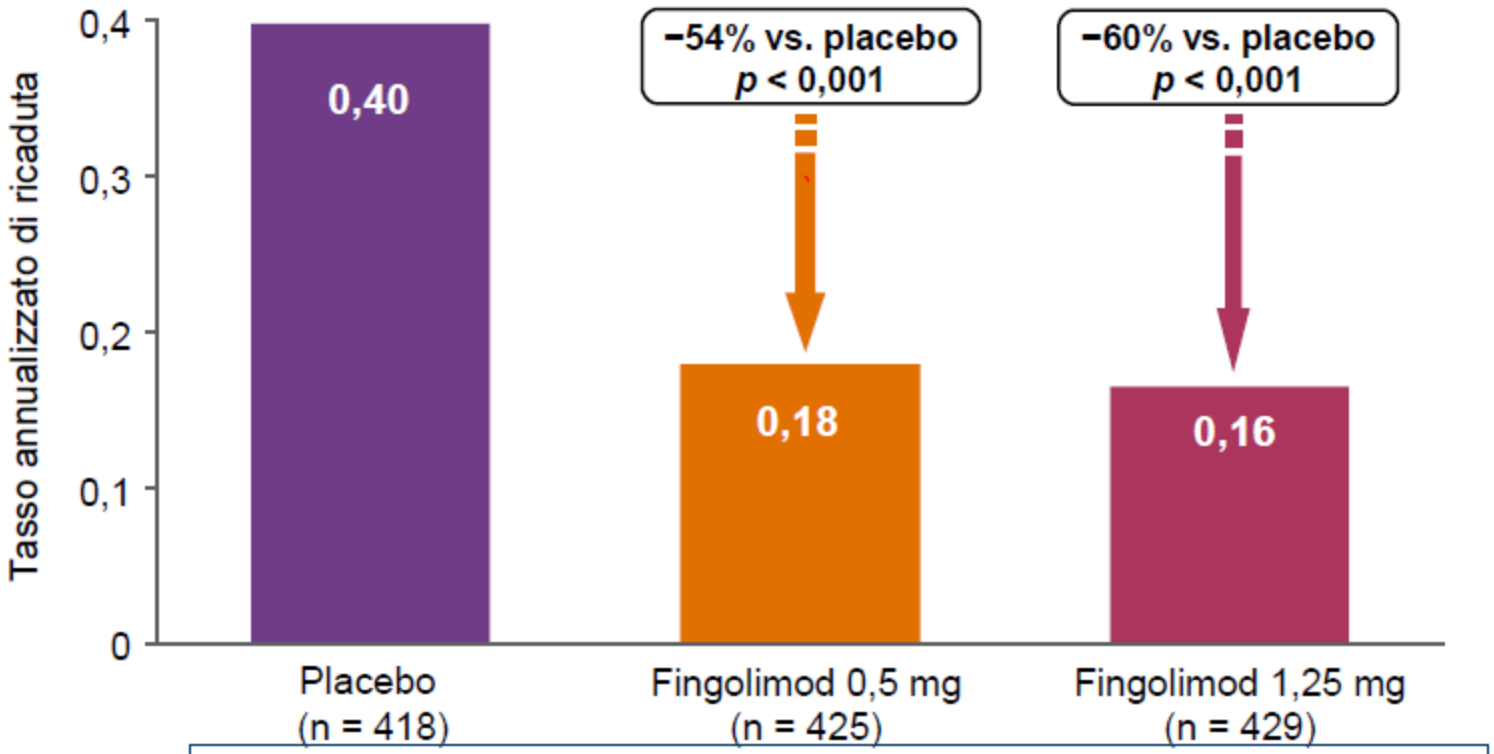
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis

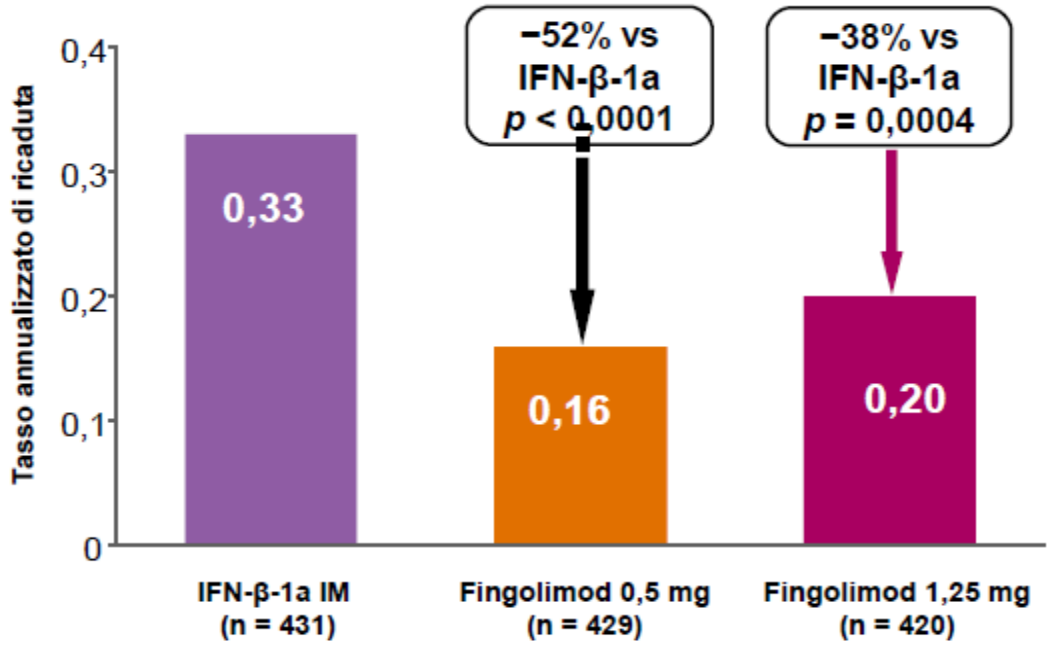
Jeffrey A. Cohen, M.D., Frederik Barkhof, M.D., Giancarlo Comi, M.D., Hans-Peter Hartung, M.D., Bhupendra O. Khatri, M.D., Xavier Montalban, M.D., Jean Pelletier, M.D., Ruggero Capra, M.D., Paolo Gallo, M.D., Guillermo Izquierdo, M.D., Klaus Tiel-Wilck, M.D., Ana de Vera, M.D., James Jin, Ph.D., Tracy Stites, Ph.D., Stacy Wu, M.D., Shreeram Aradhye, M.D., and Ludwig Kappos, M.D., for the TRANSFORMS Study Group*

FREEDOMS : tasso annualizzato di ricaduta



ARR ridotto sia nei pazienti naïve sia nei pazienti precedentemente trattati (*p < 0,01* per tutti i confronti)

TRANSFORMS: tasso annualizzato di ricaduta



Riduzione del tasso annualizzato di ricaduta superiore al 50% al dosaggio di 0.5 mg rispetto a IFN-β-1a

Popolazione ITT. Modello di regressione binomiale negativa aggiustato per le covariate: gruppo di trattamento, nazione, numero di recidive nei 2 anni precedenti al basale e punteggio EDSS al basale; recidive confermate; $p = 0,159$ per fingolimod 0,5 vs. 1,25 mg

Cohen *et al. NEJM* 2010;362(5):402–15

SIDE EFFECTS

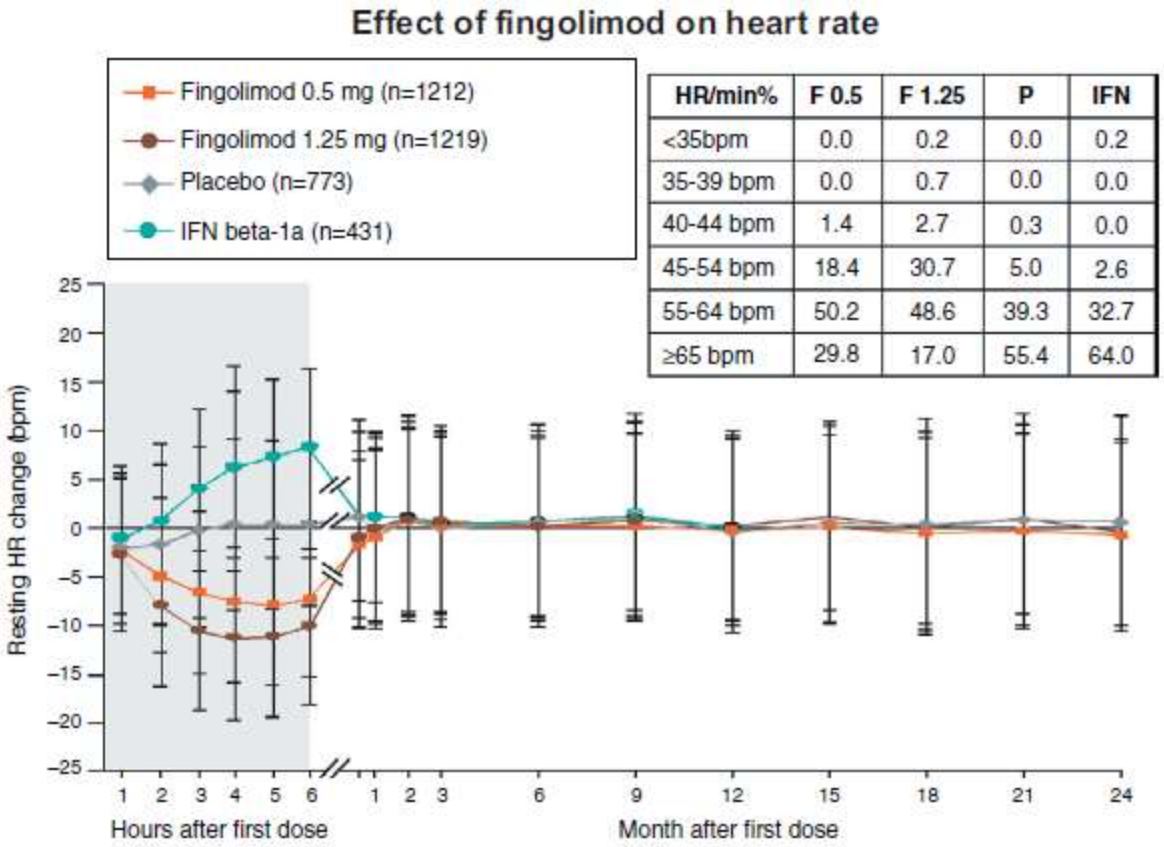
Comprehensive Safety Program with Identified and Manageable Risks

- Largest safety database in MS for an NDA submission
- Over 2600 multiple Sclerosis patients
- More than 4500 patient-years of exposure
- 1224 treated for more than 2 years and 135 treated for more than 5 years

Special areas of safety interest have been identified and studied

- Heart rate and blood pressure
- Liver enzymes
- Macular edema
- Infections
- Malignancy
- Polmonary
- Dose-dependent effects associated with fingolimod use at higher dose

W Collins, Safety Lead, Fingolimod Drug Safety & Epidemiology



HR/min%	F 0.5	F 1.25	P	IFN
<35bpm	0.0	0.2	0.0	0.2
35-39 bpm	0.0	0.7	0.0	0.0
40-44 bpm	1.4	2.7	0.3	0.0
45-54 bpm	18.4	30.7	5.0	2.6
55-64 bpm	50.2	48.6	39.3	32.7
≥65 bpm	29.8	17.0	55.4	64.0

Figure 1 Effects of fingolimod on heart rate: pooled analysis of the FREEDOMS, FREEDOMS II and TRANSFORMS studies. Results are expressed as mean ± standard deviation. The inserted table shows the minimum heart rate (HR) recorded in the first six hours after the first dose of fingolimod. F: fingolimod; IFN: interferon; IFN beta-1a: interferon beta-1a. Adapted from DiMarco et al.[46]

Table 1 Characteristics of bradycardia and atrioventricular conduction disturbances induced by the first dose of fingolimod: pooled analysis of the FREEDOMS and TRANSFORMS trials.

Bradycardia (%)	Fingolimod 0.5 mg/day (n=1212)	Fingolimod 1.25 mg/day[a] (n=1219)	Placebo (n=773)	IFN beta-1a (n=431)
Bradycardia symptoms				
All	0.6	2.1	0.1	0.0
Mild	0.4	1.2	0.1	0.0
Moderate	0.2	0.7	0.0	0.0
Severe	0.0	0.2	0.0	0.0
Treated bradycardia	2.9	5.2	0.0	0.0
Drug discontinued permanently	0.1	0.4	0.3	0.0
Atrioventricular conduction disturbances[b] (%)				
First-degree AVB	4.7	9.7	1.7	2.9
Mobitz type I AVB	0.2	1.0	0.0	0.0
Second-degree AVB, 2:1 AVB	0.0	0.2	0.0	0.0
Mobitz type II AVB or third-degree AVB	0.0	0.0	0.0	0.0

AVB: atrioventricular block; IFN beta-1a: interferon beta-1a.

[a] The only fingolimod dose approved for the treatment of MS is 0.5 mg/day. In the extension phase of the TRANSFORMS trial, there was one case of transient third-degree AVB after the first dose of 1.25 mg.

[b] Detected by electrocardiogram performed six hours after the first dose.

Table 3 First atrioventricular conduction abnormality within 24 hours of the first dose of fingolimod: analysis of the FREEDOMS II Holter subgroup.

Anomaly (%)	Fingolimod 0.5 mg/day (n=351)	Fingolimod 1.25 mg/day[a] (n=360)	Placebo (n=346)
Any AVB degree ≥2			
0–6 hours	3.1	5.0	0.0
>6–12 hours	0.3	1.4	0.0
>12 hours	0.6	0.3	2.0
Second-degree AVB, Mobitz I			
0–6 hours	2.6	5.0	0.0
>6–12 hours	0.6	1.4	0.0
>12 hours	0.6	0.3	2.0
Second-degree AVB, 2:1 AVB			
0–6 hours	1.4	2.5	0.0
>6–12 hours	0.0	0.8	0.0
>12 hours	0.6	0.0	0.0

AVB: atrioventricular block.

[a] The only fingolimod dose approved for the treatment of MS is 0.5 mg/day.

J Neurol (2014) 261:267–276
DOI 10.1007/s00415-013-7115-8

ORIGINAL COMMUNICATION

Assessment of cardiac safety during fingolimod treatment initiation in a real-world relapsing multiple sclerosis population: a phase 3b, open-label study

Ralf Gold · Giancarlo Comi · Jacqueline Palace · Arno Siever · Rebecca Gottschalk · Mahendra Bijarnia · Philipp von Rosenstiel · Davorka Tomic · Ludwig Kappos · For the FIRST Study Investigators

Received: 11 September 2013 / Accepted: 12 September 2013 / Published online: 13 November 2013

Abstract The aim of this study was to evaluate short-term safety and tolerability of fingolimod in a real-world population with relapsing multiple sclerosis, focusing on cardiac safety during treatment initiation. Patients received fingolimod 0.5 mg once daily for four months. Patients excluded from the pivotal studies with certain pre-existing cardiac conditions or baseline cardiac findings (PCCs), and those receiving beta blockers (BBs) and/or calcium channel blockers (CCBs), were eligible. Heart rate (HR) and electrical conduction events were monitored using ambulatory electrocardiography for at least 6 h after the first dose. Of 2,417 enrolled patients, 2,282 (94.4 %) completed the study. Fingolimod initiation was associated with a transient, mostly asymptomatic decrease in HR. Bradycardia adverse events occurred in 0.6 % of patients and were more frequent in individuals receiving BBs/CCBs (3.3 %) than in other patient subgroups (0.5–1.4 %); most events were asymptomatic, and all patients recovered without pharmacological intervention. In the 6 h post-dose, the incidences of Mobitz type I second-degree atrioventricular block (AVB) and 2:1 AVB were higher in patients with PCCs (4.1 and 2.0 %, respectively) than in those without (0.9 and 0.3 %, respectively); at pre-dose screening, patients with PCCs had the same incidence of Mobitz type I second-degree AVB (4.1 %) and a slightly lower incidence of 2:1 AVB (0.7 %) than 6 h post-dose. All recorded conduction abnormalities were asymptomatic. This study adds to the evidence showing that cardiac effects during fingolimod initiation remain consistent with those known from previous, controlled studies, even if patients with PCCs are included.

Keywords Fingolimod · Multiple sclerosis · Safety · Tolerability

Table 2 Incidence of bradycardia and atrioventricular conduction disturbances induced by the first dose of fingolimod in the FIRST trial.

Bradycardia in the initial six hours after first dose of fingolimod[a]			
Patients (n, %)	All (n=1219)	With cardiac risk factors (n=271)	Taking BBs or CCBs (n=78)
HR <45 bpm	16 (1.3)	12 (4.4)	2 (2.5)
HR ≤40 bpm	3 (0.2)	2 (0.7)	0 (0.0)
HR <30 bpm	0 (0.0)	0 (0.0)	0 (0.0)
Monitoring extended after 6 hours	40 (3.3)	15 (5.5)	3 (3.8)
Discharged after hour 7	31 (2.5)	12 (4.4)	3 (3.8)
Holter findings 6 hours before and 6 hours after first dose of fingolimod			
Patients (n, %)	No cardiac risk factors (n=2120)	With cardiac risk factors (n=295)	Taking BBs or CCBs (n=120)
6 hours before			
Mobitz I	2 (0.1)	11 (3.7)	0 (0.0)
2:1 AVB	0 (0.0)	2 (0.7)	0 (0.0)
6 hours after			
Mobitz I	18 (0.8)	13 (4.4)	0 (0.0)
2:1 AVB	6 (0.3)	5 (1.7)	0 (0.0)
Events before and after first dose	6 (0.3)	5 (1.7)	0 (0.0)
De novo events only after first dose	24 (1.1)	12 (4.0)	0 (0.0)

BBs: beta-blockers; CCBs: calcium channel blockers; HR: heart rate.
Criteria for extension of monitoring (any of the following): (1) HR at 6 h ≤80% of baseline HR; (2) HR at 6 h is the nadir; (3) symptomatic bradycardia.

[a] Bradycardia events evaluated in the subgroup of patients monitored in the FIRST study.

Laroni et al. BMC Neurology 2014, 14:65
http://www.biomedcentral.com/1471-2377/14/65

BMC Neurology

RESEARCH ARTICLE Open Access

Safety of the first dose of fingolimod for multiple sclerosis: results of an open-label clinical trial

Alice Laroni[1], Davide Brogi[1], Vincenzo Brescia Morra[2], Leonello Guidi[3], Carlo Pozzilli[4], Giancarlo Comi[5], Alessandra Lugaresi[6], Renato Turrini[7], Debora Raimondi[7], Antonio Uccelli[1], Giovanni Luigi Mancardi[1*] and on behalf of the EAP Investigators

Abstract

Background: In patients with relapsing-remitting MS (RRMS) fingolimod prevents disease relapses and delays disability progression. First dose administration of fingolimod is associated with a transient, dose-dependent decrease in heart rate (HR) in the 6 hours after drug intake.
The aim of the study is to to assess safety and tolerability of the first dose of fingolimod in a cohort of Italian patients with RRMS without alternative therapeutic options.

Methods: Open-label, single arm, multicentre study. After the first dose of fingolimod, patients were observed for 6 hours and had their vital signs monitored hourly. Extended on-site monitoring was provided when required.

Results: Of the 906 patients enrolled in the study, most (95.2%) did not experience any adverse event (AE) following fingolimod administration. Cardiovascular AEs occurred in 18 patients and included bradycardia (1.3%), first-and second-degree atrioventricular block (0.1% and 0.2%), palpitations (0.1%), sinus arrhythmia (0.1%) and ventricular premature beats (0.1%). All events were self-limiting and did not require any intervention. Extended monitoring was required in 34 patients.

Conclusions: These results, in a population who better resembled real-world clinical practice in terms of concomitant diseases and medications, are consistent with previous clinical trials and confirmed that the first dose administration of fingolimod is generally safe and well tolerated.

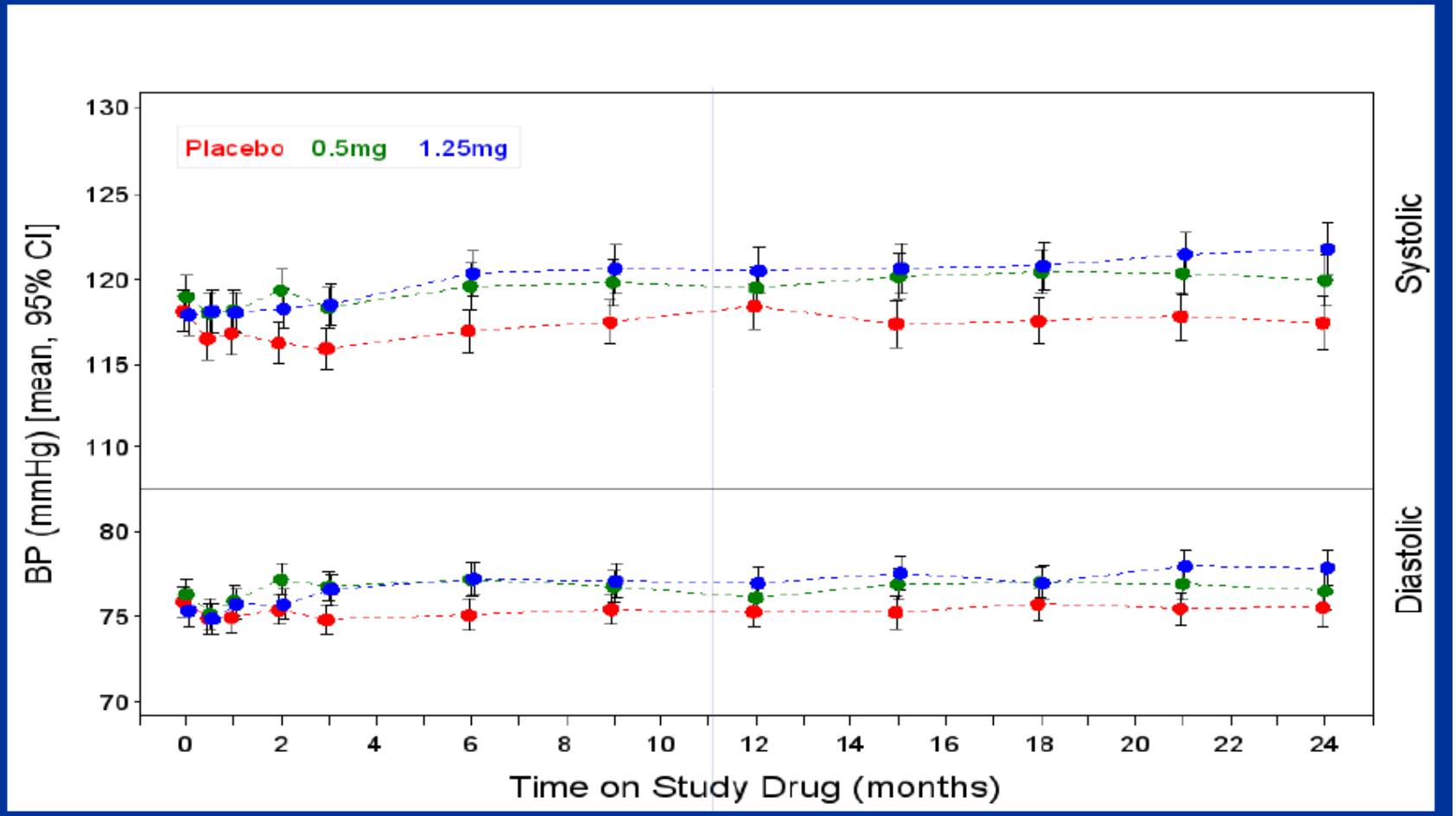
Trial registration: EudraCT 2011-000770-60

Keywords: Atrioventricular block, Bradycardia, Multiple sclerosis, Fingolimod, Safety, Tolerability

Safety Areas of Special Interest

- Pharmacodynamic effects:
- Blood Pressure increase

Systolic & Diastolic Blood Pressure over Time



2301 safety population

Patients with Increase in Blood Pressure

All studies Fingolimod

Systolic BP	0,5 mg N=1176	1,25 mg N=1302
≥160 mmHg	3,4	6,1
≥20 mmHg from BS	27	32
Diastolic BP		
≥100 mmHg	6,9	10
≥15 mmHg from BS	24,7	29

W Collins, Safety Lead, Fingolimod Drug Safety & Epidemiology

Overall Assessment of Benefit-Risk

Benefit

- **Efficacy on all relevant measures compared to placebo over 2 years**
- **Efficacy compared to 1-line therapy (over 1 year)**
- **Oral formulation leads to enhanced convenience, tolerability and potentially adherence to therapy**

Risk

- **Heart rate, blood pressure, macular edema, liver enzymes, infections, pregnancy**

- GILENYA non è raccomandato nei pazienti con:
  - blocco atrio-ventricolare di secondo grado tipo Mobitz II o di grado superiore
  - sindrome del nodo del seno
  - blocco seno-atriale
  - prolungamento del tratto QTc >470 msec (donne) o >450 msec (uomini)
  - cardiopatia ischemica compresa angina pectoris
  - malattia cerebrovascolare
  - storia di infarto del miocardio
  - insufficienza cardiaca congestizia
  - storia di arresto cardiaco
  - grave apnea notturna
  - storia di bradicardia sintomatica
  - storia di sincope ricorrente
  - ipertensione non controllata

  Se si prende in considerazione di iniziare il trattamento con GILENYA in questi pazienti, i benefici attesi devono essere superiori ai rischi potenziali e si deve consultare un cardiologo per definire il monitoraggio adeguato. Si raccomanda di prolungare il monitoraggio almeno sino al mattino successivo.

- GILENYA non è raccomandato in pazienti già in trattamento con antiaritmici di classe IA o di classe III.

- GILENYA non è raccomandato in pazienti già in trattamento con medicinali che diminuiscono la frequenza cardiaca. Se si prende in considerazione di iniziare il trattamento con GILENYA in questi pazienti, i benefici attesi devono essere superiori ai rischi potenziali e si deve consultare un cardiologo per valutare il passaggio ad altri medicinali che non riducano la frequenza cardiaca o, qualora non fosse possibile, per valutare un adeguato monitoraggio. Si raccomanda di prolungare il monitoraggio almeno sino al mattino successivo.

La checklist per il medico deve contenere i seguenti messaggi chiave:

- Requisiti per il monitoraggio all'inizio del trattamento

  Prima della prima dose

  - Eseguire un elettrocardiogramma basale prima della prima dose di GILENYA.
  - Misurare la pressione arteriosa prima della prima dose di GILENYA.
  - Eseguire un esame della funzionalità epatica prima di iniziare il trattamento.
  - Predisporre una visita oftalmologica prima di iniziare il trattamento con GILENYA per i pazienti con diabete mellito o con storia di uveite.

  Fino a 6 ore dopo la prima dose

  - Monitorare il paziente per 6 ore dopo la somministrazione della prima dose di GILENYA per verificare l'insorgenza di segni e sintomi di bradicardia, compresi il controllo ad ogni ora del battito e della pressione arteriosa. Si raccomanda il monitoraggio elettrocardiografico continuo (in tempo reale).
  - Eseguire un elettrocardiogramma alla fine del periodo di 6 ore di monitoraggio.

  Dalla 6ª all'8ª ora dopo la prima dose

  - Se, al termine delle 6 ore, la frequenza cardiaca raggiunge il valore minimo dopo la somministrazione della prima dose, prolungare il monitoraggio della frequenza cardiaca almeno per altre 2 ore e fino a quando la frequenza cardiaca non aumenti nuovamente.

Fingolimod
Profilo di sicurezza

- Bradicardia transitoria della frequenza cardiaca alla prima somministrazione di fingolimod

  Bradicardia sintomatica lieve (sonnolenza e vertigini) in <1% dei pazienti, risolta in 24 ore senza intervento farmacologico
- Incremento della pressione arteriosa media (2-3 mm Hg) durante i primi 6 mesi di trattamento
- Edema maculare

  –<1% nei primi 4 mesi di trattamento
- Incremento asintomatico e reversibile del livello ematico di enzimi epatici

Fatal infections (herpes encephalitis primary disseminated varicella) in MS patients treated with FTY

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

L'Agenzia Europea dei Medicinali suggerisce nuove raccomandazioni per una migliore gestione del rischio di effetti avversi sul cuore con Gilenya.

Per questa revisione , il CHMP ha valutato tutti i dati disponibili sulla sicurezza cardiaca di Gilenya, compresi i report di 15 casi di morte improvvisa o inspiegabile di pazienti trattati con Gilenya.
Il Comitato ha evidenziato che la maggior parte delle morti e dei problemi cardiovascolari si era verificato in pazienti con storia di problemi cardiovascolari o che assumevano altri farmaci.

Aug 29, 2013 - FDA is reporting a case of PML in a patient with MS taking fingolimod.

This is the first PML case reported in a patient who wasn't treated previously with natalizumab. Novartis reported a case of PML in April 2012 in a patient receiving fingolimod, but that patient had previously been treated for more than 3 years with natalizumab before switching to fingolimod.

Rischio CV e sclerosi multipla

CNS & Neurological Disorders - Drug Targets, 2013, *12*, 104-111

The Prevalence of the Classical and Non-Classical Cardiovascular Risk Factors in Multiple Sclerosis Patients

Zohara Sternberg[*,1], Christopher Leung[1], Daniel Sternberg[1], Fan Li[2], Yuval Karmon[1], Kailash Chadha[3] and Elad Levy[4]

[1]*Department of Neurology, Baird MS Center, Buffalo Medical Center, 100 High St. Buffalo, NY, 14203, USA*

[2]*Department of Electrical Engineering, Bell Hall, University of Buffalo, 3435 Main Street, Buffalo, NY 14214, USA*

[3]*Department of Molecular & Cellular Biology, Roswell Park Cancer Institute, Buffalo, NY 14263, USA*

[4]*Department of Neurosurgery, Buffalo Medical Center, Buffalo, NY 14203, USA*

Abstract: *Background*: Inflammation is known to play a role in cererovascular risk. Multiple sclerosis (MS) is a neurodegenerative disease that is initially characterized by inflammatory changes in the brain. We hypothesized that due to chronic inflammation, MS patients would present with a higher levels of cardiovascular (CV) risk factors than non-MS patients.

Methods: We performed a retrospective chart review on 206 MS patients and 142 control patients suffering from meningiomas and acoustic neuromas, non inflammatory, non autoimmune diseases of the brain. The obtained data included fasting lipid profiles, plasma glucose, systolic and diastolic blood pressure (BP), serum levels of homocysteine and uric acid, data on iron status, smoking habit, and list of medications. In addition, data on indicators of MS disease severity was obtained for MS patients.

Results: MS patients had significantly higher total plasma cholesterol, $p = 0.01$, and plasma high density lipoprotein, $P < 0.001$, but lower plasma glucose, $P < 0.001$, and systolic BP, $P = 0.001$, than non-MS patients. In addition, MS patients had lower erythrocyte sedimentation rate and serum vitamin B12, but higher serum folic acid and vitamin D_3 than non-MS patients. A positive correlation was observed between plasma glucose and the extended disability status scale (EDSS), $P = 0.008$, and between plasma glucose and the rate of clinical relapse, $P = 0.001$.

Conclusion: The MS pathophysiology may be among factors for the lower CV risk factors in MS patients. Future studies should examine whether the chronic use of many pharmacological agents influence CV risk factors in MS patients.

Keywords: Blood pressure, dyslipidemia, homocysteine, inflammation, multiple sclerosis, plasma glucose.

The Prevalence of the Classical and Non-Classical Cardiovascular Risk Factors in Multiple Sclerosis Patients

Zohara Sternberg[*,1], Christopher Leung[1], Daniel Sternberg[1], Fan Li[2], Yuval Karmon[1], Kailash Chadha[3] and Elad Levy[4]

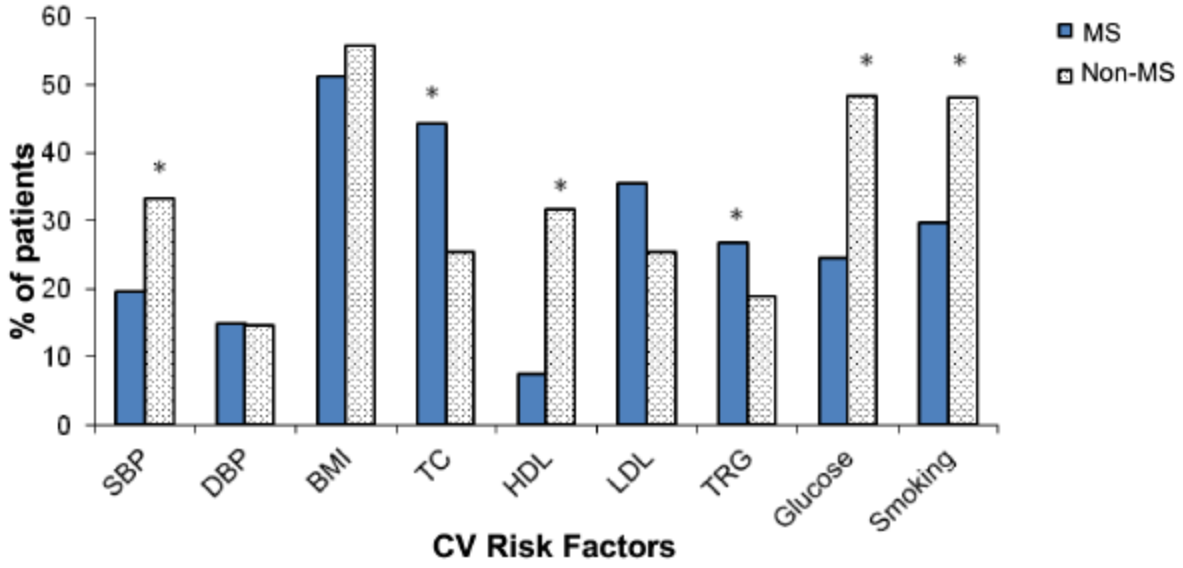


Fig. (1A). The percentages of MS and non-MS patients presenting with CV risk factors.

Classical CV Risk Factors in MS and Non-MS Patients

Classical CV Risk Factors	MS (Means ±SD)	Non-MS (Means ±SD)	P-Values
Systolic BP (mmHg)	122.4±17.5 (78-185)	127.3±17.1 (98-162)	0.001
Diastolic BP (mmHg)	77.7±11.2 (55-110)	75.5±12.3 (46-99)	0.1
BMI (kg/m2)	26.8±5.8 (16.5-55.9)	27.6±6.3 (17-51.2)	0.3
TC (mg/dL)	201.4±40.9 (115-323)	174.6±33.8(100-237)	0.01
HDL (mg/dL)	55.0±14.6(27-94)	46.4±15.0(26-97)	<0.001
LDL (mg/dL)	118.7±33.9(53-220)	106.6±27.8(43-161)	0.2
TRG (mg/dL)	133.7±98.3(19-490)	112.1±47.3(39-235)	0.4
Glucose (mg/dL)	94.2±21.5(63-218)	108.5±31.0(55-217)	<0.001

Non-Classical Risk Factors	Normal Ranges	MS	Non-MS	P-Values
ESR (mm/hr)	12.0-23.0	10.6±9.3 (1-41)	18.5±19.6 (2-81)	0.04
Homocysteine (µmol/L)	8.0-12.0	8.4±2 (6-12)	NA	
Uric acid (mg/dL)	3.5-8.5	4.6±1.3 (2.4-6)	NA	
Folic acid (ng/mL)	2.7-17.0	18.2±5.8 (6-24)	14.8±6.0 (5-24)	0.04
Vitamin B_{12} (pg/mL)	200-900	503.4±239 (152-1273)	666.7±314 (213-1200)	0.03
Vitamin D_3 (ng/mL)	20-56	30.5±14.0 (4-60)	15.2±5.6 (10-25)	<0.001
Iron (µg/dL)	26-198	74.2±51 (21-208)	NA	
Ferritin (ng/mL)	12.0-250	74.0±72.3 (9-263)	NA	
Total Iron-Binding Capacity (µg/dL)	262-474	380±47 (288-423)	NA	

Clin Auton Res (2005) 15:213–218
DOI 10.1007/s10286-005-0274-7

RESEARCH ARTICLE

Emmanuel O. Sanya
Marcin Tutaj
Clive M. Brown
Nursel Goel
Bernhard Neundörfer
Max J. Hilz

Abnormal heart rate and blood pressure responses to baroreflex stimulation in multiple sclerosis patients

Abstract Cardiovascular autonomic neuropathy has been previously reported in patients with multiple sclerosis (MS) using standard reflex tests. However, no study has separately evaluated both parasympathetic and sympathetic cardiovascular autonomic regulation. We therefore assessed the baroreflex-mediated vagal and sympathetic control of the heart rate and sympathetic control of the blood vessels in MS patients using sinusoidal neck stimulation.

We studied 13 multiple sclerosis patients aged 28–58 years and 18 healthy controls aged 26–58 years. The carotid baroreflex was stimulated by sinusoidal neck suction (0 to −30 mmHg) at 0.1 Hz to assess the autonomic control of the heart and blood vessels, and at 0.2 Hz to assess the vagal control of the heart. Continuous recordings were made of blood pressure, electrocardiographic RR-interval and respiration, with breathing paced at 0.25 Hz. Spectral analysis was used to evaluate the magnitude of the low frequency (LF, 0.03–0.14 Hz) and high frequency (HF, 0.15–0.50 Hz) oscillations in RR-interval and blood pressure in response to the sinusoidal baroreceptor stimulation. Responses to the applied stimulus were assessed as the change in the spectral power of the RR-interval and blood pressure fluctuations at the stimulating frequency from the baseline values.

The increase in the power of 0.1 Hz RR-interval oscillations during the 0.1 Hz neck suction was significantly smaller ($p < 0.01$) in the MS patients (4.47 ± 0.27 to 5.62 ± 0.25 ln ms^2) than in the controls (4.12 ± 0.37 to 6.82 ± 0.33 ln ms^2). The increase in the power of 0.1 Hz systolic BP oscillations during 0.1 Hz neck suction was also significantly smaller ($p < 0.01$) in the MS patients (0.99 ± 0.19 to 1.96 ± 0.39 mmHg^2) than in the healthy controls (1.27 ± 0.34 to 9.01 ± 4.10 mmHg^2). Neck suction at 0.2 Hz induced RR-interval oscillations at 0.2 Hz that were significantly smaller ($p < 0.05$) in the patients (3.22 ± 0.45 ln ms^2) than in the controls (5.27 ± 0.29 ln ms^2). These results indicate that in MS patients, baroreflex dysfunction is not only restricted to the cardiovagal limb of the baroreflex, but that the sympathetic modulation of the blood vessels is also affected.

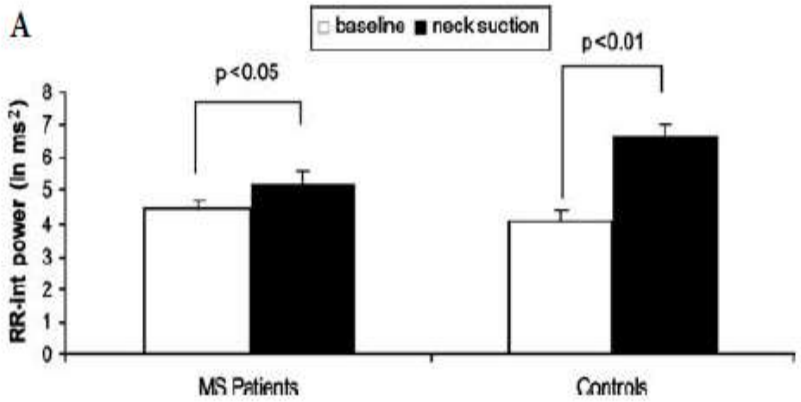
Key words multiple sclerosis · baroreflex · heart rate · blood pressure · neck suction

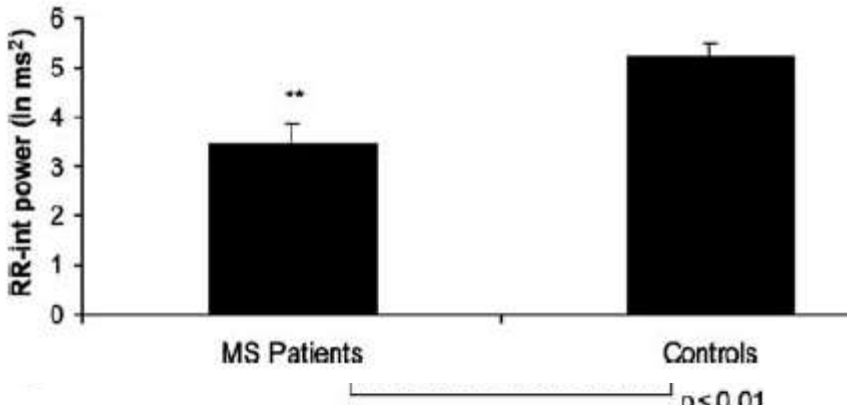
Received: 10 March 2003
Accepted: 28 February 2005

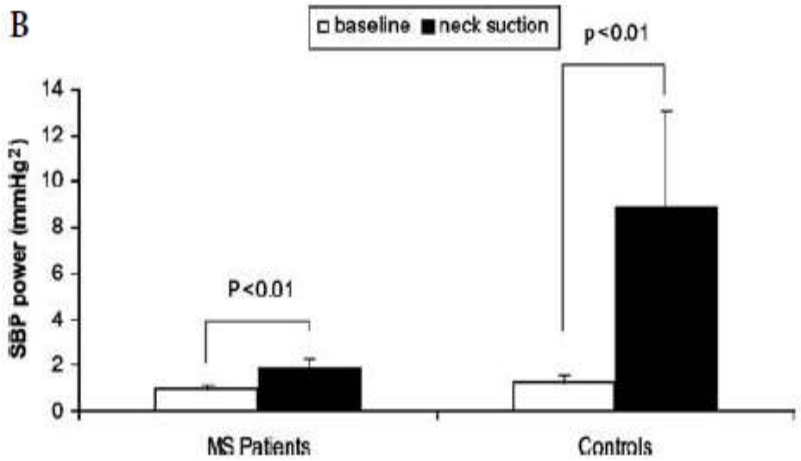
E. O. Sanya, MD · M. Tutaj, MD · C. M. Brown, PhD · N. Goel · B. Neundörfer, MD · M. J. Hilz, MD
Autonomic Laboratory
Dept. of Neurology
University of Erlangen-Nuremberg
Erlangen, Germany

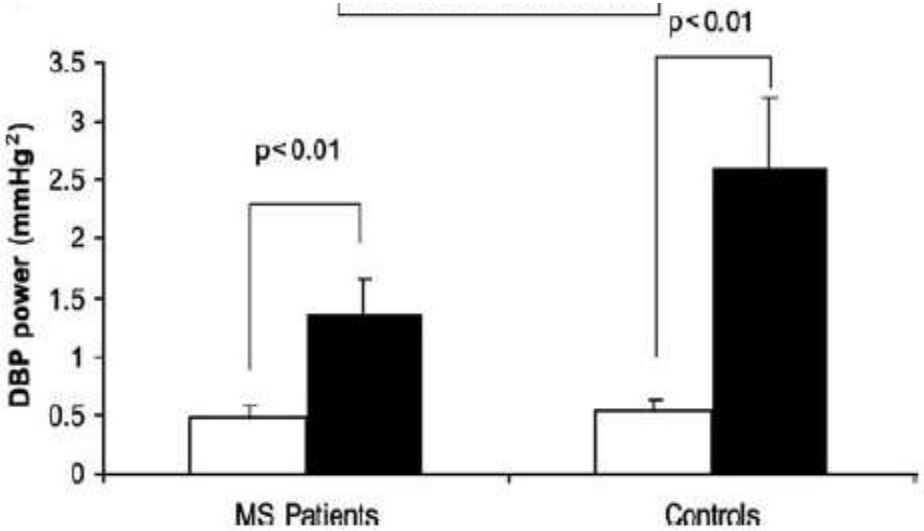
Dr. E. O. Sanya (✉)
Dept. of Medicine
University of Ilorin Teaching Hospital
PMB1459
Ilorin Kwara State, Nigeria
Tel.: +234-31/225-621
Fax: (efax) 13094096081
E-Mail: emanuelosanya@yahoo.com

M. Tutaj, MD
Dept. of Neurology
Jagiellonian University
Krakow, Poland


A
baseline
neck suction
p<0.05
p<0.01
RR-int power (ln ms²)
MS Patients
Controls


RR-int power (ln ms²)
**
MS Patients
Controls


B
baseline
neck suction
p<0.01
P<0.01
SBP power (mmHg²)
MS Patients
Controls


p<0.01
p<0.01
DBP power (mmHg²)
MS Patients
Controls

ORIGINAL ARTICLE

Prevalence of overweight, obesity and metabolic syndrome components in multiple sclerosis patients with significant disability

O. Pinhas-Hamiel[a,b], M. Livne[b,c], G. Harari[d] and A. Achiron[b,c]

[a]*Pediatric Endocrinology and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Ramat-Gan;* [b]*Sackler School of Medicine, Tel-Aviv University, Tel-Aviv;* [c]*Multiple Sclerosis Center, Sheba Medical Center, Ramat-Gan; and* [d]*Medistat, Tel-Aviv, Israel*

Keywords:
cardiovascular risk, metabolic syndrome, multiple sclerosis, obesity, overweight, waist circumference

Received 30 January 2015
Accepted 30 March 2015

European Journal of Neurology 2015, **0**: 1–5

doi:10.1111/ene.12738

Background and purpose: Information about metabolic comorbidities in patients with multiple sclerosis (MS) is scarce. Our aim was to examine the prevalence of the metabolic syndrome (MetS) and its components in patients with long duration of MS and significant disability.

Methods: Demographic and clinical data, weight, height, waist circumference, blood pressure, and levels of fasting glucose, triglycerides and high density lipoprotein cholesterol (HDL-C) were obtained from 130 MS patients with Extended Disability Status Scale (EDSS) score ≥3.0.

Results: Seventy-two percent were female, mean ± SD age 55.8 ± 6.0, range 45–65 years, disease duration 18.2 ± 10.1 years, EDSS 5.5 ± 1.0. Obesity [body mass index (BMI) ≥ 30 kg/m^2] was present in 18.5% and overweight (BMI 25.0–29.9 kg/m^2) in 34.6%. The prevalence of the MetS was 30% with no gender difference. Fifty-six percent had central obesity by waist circumference, 28% treated hypertension, 45.8% elevated blood pressure, 11% type 2 diabetes mellitus, 31.4% treated dyslipidemia, 28.8% elevated triglyceride levels and 31.4% had low HDL-C. MS patients with MetS were significantly older (59.0 ± 5.5 vs. 53.8 ± 5.5, $P < 0.0001$) and heavier (BMI 29.0 ± 6.9 vs. 25.1 ± 4.7, $P = 0.0009$). There were no differences between the groups in neurological disability by the EDSS (5.7 ± 1.0 vs. 5.4 ± 1.0), disease duration (18.4 ± 9.9 vs. 18.2 ± 10.2 years) and number of steroid courses received (6.6 ± 9.5 vs. 6.3 ± 8.4).

Conclusions: Compared to the general population, adult disabled MS patients had lower rates of obesity and overweight, as assessed by BMI. Despite these reduced rates, the prevalence of the MetS was similar to the general population. Specifically higher rates of increased waist circumference were found, suggesting that the lower BMI may be misleading in terms of health risk.

EUROPEAN JOURNAL OF NEUROLOGY

	Normal weight BMI < 25 kg/m^2 $N = 61$	Overweight BMI ≥ 25 < 30 kg/m^2 $N = 45$	Obese BMI ≥ 30 kg/m^2 $N = 24$	P
Age (years)	54.3 ± 5.8	56.7 ± 6.1	57.7 ± 5.9	0.029
EDSS	5.4 ± 1.0	5.4 ± 1.0	5.8 ± 0.8	0.192
Disease duration (years)	19.1 ± 9.5	18.4 ± 10.8	15.8 ± 10.3	0.392
No. of steroid courses				
Mean ± SD	8.3 ± 10.6	4.2 ± 5.9	5.9 ± 1.5	0.052
Median (CI)	4 (5.6–11)	2 (2.4–5.9)	2.5 (2.8–8.9)	
Waist circumference > 102 cm (men) or 88 cm (women) (%)	21	82	100	0.0001
Hypertension (%)	15	29	58	0.0003
Hyperglycemia (%)	6.6	6.7	8.3	0.497
Type 2 diabetes (%)	7	9	21	0.135
Triglycerides > 150 mg/dl (%)	20	31	33	0.497
HDL-C < 40 mg/dl (%)	26	31	29	0.823
Treated dyslipidemia (%)	25	24	46	0.07
Metabolic syndrome (%)	18	31	58	0.0013

BMI, body mass index; EDSS, Extended Disability Status Scale; CI, confidence interval; HDL-C, high density lipoprotein cholesterol.

RESEARCH PAPER

Cardiovascular risk factors are associated with increased lesion burden and brain atrophy in multiple sclerosis

Natalie Kappus,[1] Bianca Weinstock-Guttman,[2] Jesper Hagemeier,[1] Cheryl Kennedy,[1] Rebecca Melia,[1] Ellen Carl,[1] Deepa P Ramasamy,[1] Mariya Cherneva,[1] Jacqueline Durfee,[1] Niels Bergsland,[1,3] Michael G Dwyer,[1] Channa Kolb,[2] David Hojnacki,[2] Murali Ramanathan,[4] Robert Zivadinov[1,2,5]

For numbered affiliations see end of article.

Correspondence to
Dr Robert Zivadinov, Buffalo Neuroimaging Analysis Center, MRI Clinical Translational Research Center, Department of Neurology, School of Medicine and Biomedical Sciences, 100 High St, Buffalo, NY 14203, USA; rzivadinov@bnac.net

Received 1 December 2014
Revised 26 January 2015
Accepted 4 February 2015

ABSTRACT

Background Cardiovascular (CV) risk factors have been associated with changes in clinical outcomes in patients with multiple sclerosis (MS).

Objectives To investigate the frequency of CV risks in patients with MS and their association with MRI outcomes.

Methods In a prospective study, 326 patients with relapsing–remitting MS and 163 patients with progressive MS, 61 patients with clinically isolated syndrome (CIS) and 175 healthy controls (HCs) were screened for CV risks and scanned on a 3T MRI scanner. Examined CV risks included hypertension, heart disease, smoking, overweight/obesity and type 1 diabetes. MRI measures assessed lesion volumes (LVs) and brain atrophy. Association between individual or multiple CV risks and MRI outcomes was examined adjusting for age, sex, race, disease duration and treatment status.

Results Patients with MS showed increased frequency of smoking (51.7% vs 36.5%, p=0.001) and hypertension (33.9% vs 24.7%, p=0.035) compared with HCs. In total, 49.9% of patients with MS and 36% of HCs showed ≥2 CV risks (p=0.003), while the frequency of ≥3 CV risks was 18.8% in the MS group and 8.6% in the HCs group (p=0.002). In patients with MS, hypertension and heart disease were associated with decreased grey matter (GM) and cortical volumes (p<0.05), while overweight/obesity was associated with increased T1-LV (p<0.39) and smoking with decreased whole brain volume (p=0.049). Increased lateral ventricle volume was associated with heart disease (p=0.029) in CIS.

Conclusions Patients with MS with one or more CV risks showed increased lesion burden and more advanced brain atrophy.

The progression of MS may be related to other risk factors, including underlying comorbidities.[12] Patients who reported more than one cardiovascular (CV) risk factors at the time of diagnosis had an increased chance of ambulatory disability, and the risk increased with the number of CV risk factors reported.[13] Two nationwide Danish mortality studies reported that patients with MS had more than a 30% higher risk of death due to CV disease, including cerebrovascular disease, compared with the age-matched general population.[14 15] Another Danish study showed that the risk of CV disease among patients with incident MS is relatively low, but higher than that in the general population.[16] A higher risk of death due to CV disease, excluding stroke (6%), was also reported in a study from South Wales.[17]

CV risk factors like hypertension, hyperlipidaemia and heart disease are associated with increased number of brain white matter (WM) signal abnormalities[18] and decreased grey matter (GM) volume[19–21] in the general population. A number of recent studies have investigated the relationship between individual CV risk factors and MRI measures of MS disease progression. Smoking and altered lipid profiles are positively associated with more severe MRI outcomes.[5 8 11 22 23] African-Americans, who have an increased rate of CV risk factors compared with Caucasians,[24] have been shown to have greater lesion burden and more brain atrophy in patients with MS.[25]

The primary goal of this study was to investigate the frequency of CV risk factors in a large cohort of patients with MS, compared with that of healthy controls (HCs) and patients with clinically isolated syndrome (CIS), and assess their association with MRI outcomes of disease severity.

Table 5 Analysis of covariance, adjusted by age, sex, race, disease duration and disease-modifying treatment status, showing associations between CV risk factors and MRI outcomes in the study groups

	Disease group	MRI variable	p Value*
Individual CV risk factors			
Hypertension	MS	NGMV	0.042
	MS	NCV	0.046
Heart disease	MS	NGMV	0.029
	MS	NCV	0.033
	CIS	NLVV	0.029
	RRMS	NGMV	0.044
BMI ≥25	MS	T1-LV	0.039
	RRMS	T1-LV	0.048
Smoking	MS	NBPV	0.049
Two or more overall CV risk factors	MS	NGMV	<0.001
	MS	NCV	0.003
	RRMS	NGMV	0.04
	RRMS	NCV	0.04
Hypertension and smoking	MS	NGMV	0.034
	RRMS	T2-LV	0.035
Hypertension and BMI ≥25	RRMS	NGMV	0.048
Heart disease and smoking	CIS	NLVV	0.048
Three or more overall CV risk factors	MS	NGMV	0.04
	MS	NCV	0.048
Hypertension and heart disease and BMI ≥25	RRMS	T2-LV	0.009
	PMS	LVV	0.045
Hypertension and heart disease and smoking	MS	T2-LV	0.039
	RRMS	T2-LV	0.029
	PMS	T2-LV	0.044
Hypertension and smoking and BMI ≥25	RRMS	NBPV	0.044
	RRMS	NGMV	0.047
	PMS	NLVV	0.045

*Only significant associations corrected for multiple comparisons are shown.
BMI, body mass index; CIS, clinically isolated syndrome; CV, cardiovascular; LV, lesion volume; MS, multiple sclerosis; NBPV, normalised brain parenchymal volume; NCV, normalised cortical volume; NGMV, normalised grey matter volume; NLVV, normalised lateral ventricle volume; PMS, progressive MS; RRMS, relapsing–remitting MS.

Neuro
epidemiology

Neuroepidemiology 2008;30:234–238
DOI: 10.1159/000128103

Received: October 9, 2007
Accepted: February 22, 2008
Published online: April 25, 2008

Vascular Disease among Hospitalized Multiple Sclerosis Patients

Norrina B. Allen[a] Judith H. Lichtman[a] Hillel W. Cohen[c] Jing Fang[c]
Lawrence M. Brass[a, b, †] Michael H. Alderman[c, d]

[a]Section of Chronic Disease Epidemiology, Department of Epidemiology and Public Health, Yale University School of Medicine, and [b]Department of Neurology, Yale School of Medicine, New Haven, Conn., [c]Department of Epidemiology and Population Health, and [d]Section of General Internal Medicine, Department of Medicine, Albert Einstein School of Medicine, Bronx, N.Y., USA

Key Words
Multiple sclerosis · Cardiovascular disease · Ischemic stroke

Abstract
Background: We examined the prevalence of cardiac and cerebrovascular disease among hospitalized patients with and without multiple sclerosis (MS). ***Methods:*** This study used the Statewide Planning and Research Cooperate System data set of over 15 million hospitalizations in New York City from 1988 through 2002. We identified MS patients 40–84 years of age who were hospitalized for reasons other than MS or related complications. MS patients were matched 1:2 on age, gender, race/ethnicity, and insurance. Outcomes included a principal discharge diagnosis of ischemic heart disease [International Classification of Diseases, Ninth Revision (ICD-9) 410–414], myocardial infarction (ICD-9 410), and ischemic stroke (ICD-9 434, 436). Multivariate logistic regression was used to compare vascular disease outcomes in MS and non-MS patients controlling for demographic and clinical factors. ***Results:*** Our study included 9,949 hospitalizations among MS patients and 19,898 hospitalizations for matched non-MS controls. MS patients were less likely to be hospitalized for ischemic heart disease (OR = 0.58, 95% CI = 0.51–0.66) or myocardial infarction (OR = 0.78, 95% CI = 0.64–0.96), but more likely to be hospitalized for ischemic stroke (OR = 1.66, 95% CI = 1.33–2.09) than matched non-MS controls. ***Conclusion:*** MS patients have decreased rates of hospital admission for ischemic heart disease and myocardial infarction, but increased rates of hospitalization for ischemic stroke as compared to the general non-MS population.

Introduction

Multiple sclerosis (MS) patients have recently been found to have decreased uric acid levels as compared to both the general population and patients with other neurological diseases [1, 2]. Uric acid, the end product of purine metabolism, functions as a peroxynitrite scavenger. In addition to its beneficial antioxidant properties, under certain conditions uric acid may be detrimental by acting as a proinflammatory agent and mediating endothelial dysfunction [3]. Epidemiologic studies have found that elevated uric acid levels are associated with increased risk of cardiovascular disease and stroke [4, 5]. Given that MS patients have been shown to have lower uric acid levels, we hypothesized that they may also have a lower prevalence of vascular disease. Accordingly, the goal of this

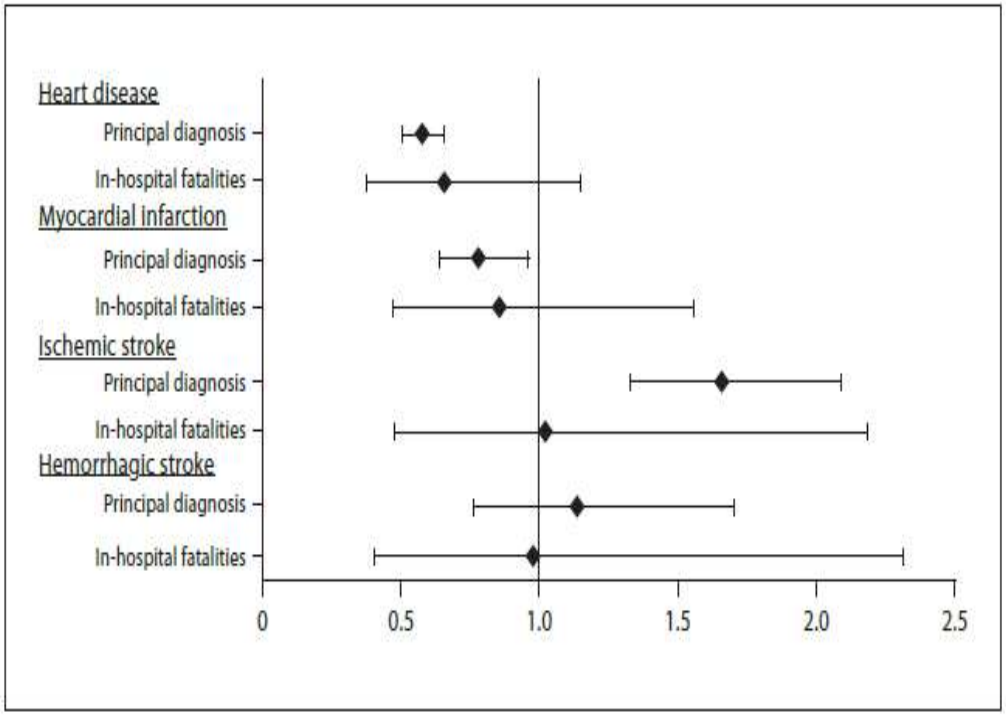


Fig. 1. ORs and 95% CIs for vascular outcomes in MS patients as compared to non-MS patients.

Table 2. ORs for vascular comorbidities in MS patients as compared to non-MS patients

Co-morbidity	MS patients (n = 9,949)		Non-MS patients (n = 19,898)		p value	OR[1]	95% CI
	n	%	n	%			
Hospitalized for IHD	355	3.57	1,422	7.15	<0.0001	0.58	0.51–0.66
In-hospital fatalities	18	5.07	46	3.23	0.097	0.66	0.38–1.15
Hospitalized for MI	142	1.43	403	2.03	0.0003	0.78	0.64–0.96
In-hospital fatalities	17	11.97	33	8.19	0.1793	0.86	0.47–1.56
Hospitalized for ischemic stroke	140	1.41	199	1.00	0.0018	1.66	1.33–2.09
In-hospital fatalities	11	8.66	17	9.39	0.5031	1.02	0.48–2.19
Hospitalized for hemorrhagic stroke	38	0.38	69	0.35	0.7523	1.14	0.76–1.71
In-hospital fatalities	8	21.05	16	23.19	0.7439	0.98	0.41–2.32

[1] Adjusted for age, sex, race/ethnicity, insurance type, length of hospitalization, admission type, hypertension, hypercholesterolemia, diabetes mellitus, and obesity.

Rischi e benefici della terapia

- Anticonvulsionanti
- Ansiolitici
- Antispastici
- Gaba-like
- Baclofen
- Benzodiazepine
- Antiaggreganti, statine e antipertensivi

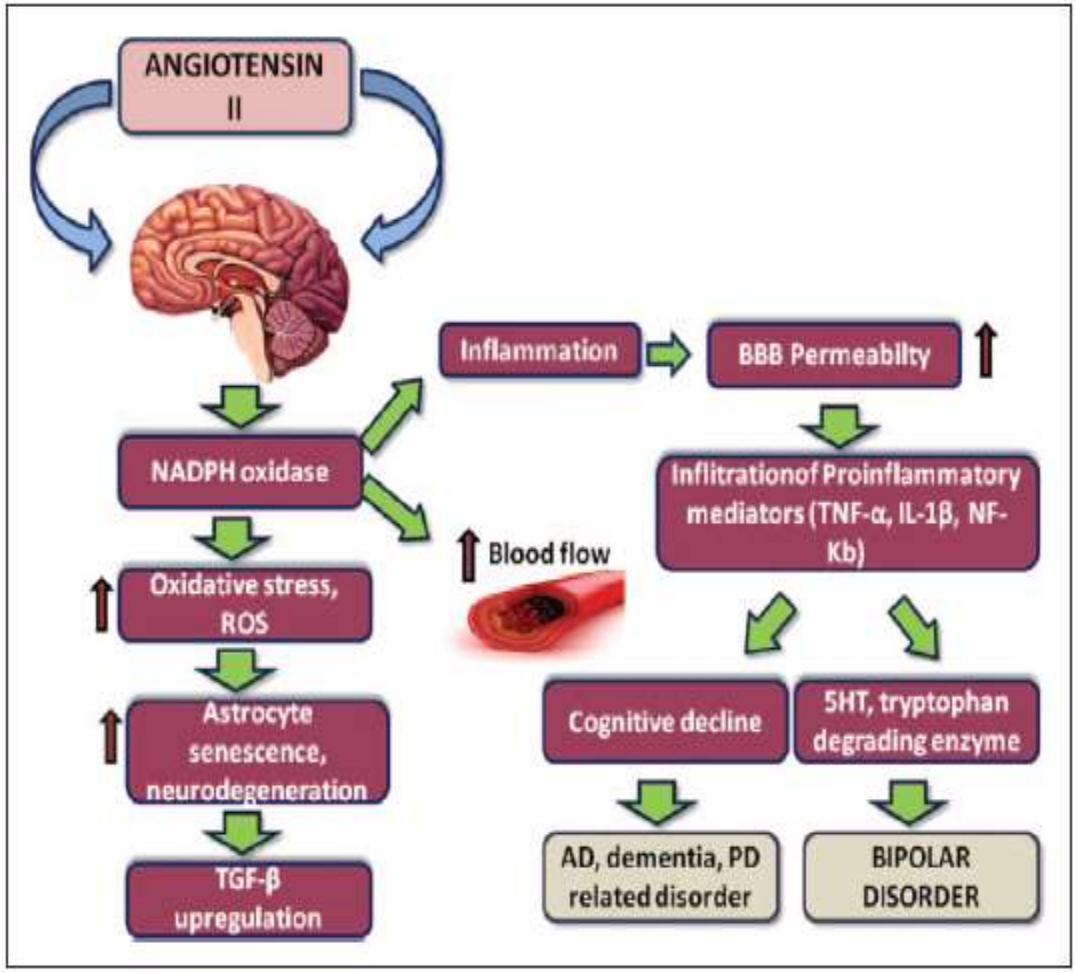


Figure 2. Role of Ang II in BD and in cognitive dysfunctions of AD and PD.

Original

ISSN 0946-1965

The effects of 1 month antihypertensive treatment with perindopril, bisoprolol or both on the ex vivo ability of monocytes to secrete inflammatory cytokines

A. Madej[1], L. Buldak[1], M. Basiak[1], W. Szkrobka[1], A. Dulawa[2] and B. Okopien[1]

[1]*Department of Internal Medicine and Clinical Pharmacology,*
[2]*Chair and Department of Anaesthesiology and Intensive Care, Medical University of Silesia, Poland*

Key words
hypertension – bisoprolol – perindopril – monocyte – cytokines

Abstract. Introduction: Monocytes are key elements in pathogenesis of atherosclerosis and inflammation. The data regarding associations between antihypertensive treatment and monocytes' function are still lacking. The aim of this study was to evaluate the influence of antihypertensive drugs (bisoprolol, perindopril or both) in patients suffering from mild to moderate hypertension. Patients and methods: The study population consisted of 67 patients divided into 3 groups (2 consisted of patients with Grade I essential hypertension and one consisted of patients with Grade II essential hypertension). At baseline and 1 month after treatment we performed 24-h ambulatory noninvasive blood pressure monitoring and measured IL-1β, IL-6, IL-10, MCP-1 and TNF-α in a medium derived from LPS-stimulated monocytes' culture. Results: Both monotherapies with bisoprolol or perindopril were equally effective in lowering blood pressure (reduction in mean 24-h systolic blood pressure 12.07 vs. 15.91 mmHg, p = 0.678). Antihypertensive treatment led to significant decrease in IL-1β, IL-6, MCP-1 and TNF-α concentration and significant rise in IL-10 level compared to the baseline levels and the decrease was associated with reduction in blood pressure. Conclusions: Bisoprolol and perindopril effectively reduced elevated blood pressure. As a result, an alteration in cytokine net was observed at the end of the study. These results support the concept of possible anti-inflammatory effects of antihypertensive drugs (e.g., perindopril and bisoprolol).

Received
January 28, 2009;
accepted
May 29, 2009

Correspondence to
Department of Internal Medicine and Clinical Pharmacology,
Medical University of Silesia, Medyków 14,
43-752 Katowice,
Poland
boolean@poczta.onet.pl

Introduction

The body of evidence about important interactions between cytokines and cardiovascular diseases is growing. Diseases that are associated with atherosclerosis (e.g., myocardial infarction, stroke or unstable angina pectoris) are characterized by increased markers of inflammation (e.g., Interleukin-1, Interleukin-6, TNF-α) [Biasucci et al. 1999, Ford and Giles 2000, Nikfardjam et al. 2000, Ridker et al. 2000]. Nevertheless, the significance of cytokines' levels and monocytes have not yet been studied thoroughly. Elevated blood pressure is also associated with increased serum concentration of proinflammatory cytokines (TNF-α, IL-6), chemokines (MCP-1) and adhesion molecules (P-selectin, ICAM-1) [Chae et al. 2001, Schillaci et al. 2003, Stumpf et al. 2005]. However, the data regarding the liaisons between antihypertensive treatment and monocyte function is still lacking. Therefore, the aim of the study was to evaluate the influence of antihypertensive treatment, consisting of β-blocker BB (bisoprolol), angiotensin-converting enzyme inhibitor, ACEI (perindopril) or both in patients with mild to moderate hypertension, on monocyte secretion of proinflammatory cytokines (IL-1β, IL-6, TNF-α) and MCP-1. Monocytes were chosen as a subject of the study, because these cells are highly associated with inflammation [Huang et al. 1999], atherosclerosis [Osterud and Bjorklid 2003], plaque formation, and are at least partially responsible for plaque instability. Both antihypertensive agents have well-documented effectiveness in hypertension and may be prescribed in monotherapy as well as politherapy. MCP-1 is an important element in atherogenesis, it promotes monocyte recruitment, adherence and transmigration of monocytes. IL-1β, IL-6 and TNF-α are potent

Table 3. Effects of antihypertensive therapies on IL-6, TNF-α, IL-1β and MCP-1.

Group	Control	Moderate HA	Mild HA (combined)	Mild HA (bisoprolol)	Mild HA (perindopril)
IL-6 (ng/ml)					
Pre	6.53 ± 1.4	13.25 ± 3.03	11.04 ± 1.46	10.48 ± 1.21	11.62 ± 1.49
Post	na	4.69 ± 3.50	6.08 ± 0.66	5.82 ± 0.39	6.35 ± 0.78
p (pre vs. control)	na	0.001	0.001	0.001	0.001
tp (pre vs. post)	na	0.006	0.002	<0.001	0.001
TNF-α (ng/ml)					
Pre	1.07 ± 0.19	2.15 ± 0.43	1.96 ± 0.35	1.93 ± 0.45	2.0 ± 0.21
Post	na	1.1 ± 0.37	1.22 ± 0.26	1.21 ± 0.27	1.23 ± 0.24
p (pre vs. control)	na	0.001	0.001	0.001	0.001
p (pre vs. post)	na	0.001	< 0.01	< 0.001	0.001
IL-1β (pg/ml)					
Pre	155.89 ± 18.44	250.39 ± 22.59	226.7 ± 25.0	221.8 ± 22.47	231.81 ± 26.97
Post	na	146.31 ± 22.64	148.09 ± 20.79	141.81 ± 21.39	154.66 ± 18.39
p (pre vs. control)	na	0.001	0.001	0.001	0.001
p (Pre vs. post)	na	0.001	0.001	0.001	0.001
MCP-1 (ng/ml)					
Pre	12.25 ± 1.55	21.29 ± 2.66	19.04 ± 3.21	19.46 ± 3.24	18.61 ± 3.21
Post	na	16.44 ± 2.91	14.18 ± 4.38	15.23 ± 4.21	13.1 ± 4.4
p (pre vs. control)	na	0.001	0.001	0.001	0.01
p (pre vs. post)	na	0.001	0.01	0.002	0.001

HA = hypertension; pre = at the beginning of the study; post = at the end of the study; na = not applicable.

European Neurology

Original Paper

Eur Neurol 2014;71:173–179
DOI: 10.1159/000355530

Received: April 10, 2013
Accepted: September 8, 2013
Published online: January 21, 2014

Effects of Inhibitors of the Renin-Angiotensin System on the Efficacy of Interferon beta-1b: A post hoc Analysis of the BEYOND Study

M. Doerner[a] K. Beckmann[b] V. Knappertz[e] L. Kappos[i] H.P. Hartung[c] M. Filippi[j]
P.W. O'Connor[i] B. Arnason[f] S. Cook[g] D. Jeffery[h] G. Comi[k] V. Limmroth[d]

Key Words
Multiple sclerosis · Renin-angiotensin system · BEYOND study · Cardiovascular comorbidity · Interferon beta · Angiotensin receptor blockers · Angiotensin-converting enzyme inhibitors · Immune system · Hypertension

Abstract

Background: In experimental autoimmune encephalomyelitis, inhibition of the renin-angiotensin system with angiotensin receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors resulted in a significantly ameliorated disease course. We evaluated the effects of ARBs and ACE inhibitors on the efficacy of interferon beta-1b in patients with relapsing-remitting multiple sclerosis (RRMS). ***Methods:*** In this post hoc analysis of the BEYOND (Betaferon Efficacy Yielding Outcomes of a New Dose) study, clinical and MRI end points were compared between patients treated with interferon beta-1b 250 or 500 µg and concomitant ARBs or ACE inhibitors and patients treated with interferon beta-1b 250 or 500 µg only (reference group). ***Results:*** Patients in the ARB group (n = 22) tended to have a higher relapse rate (0.48 vs. 0.23, p = 0.051) and a higher number of new gadolinium-enhancing lesions (0.6 vs. 0.3, p = 0.057) than patients in the reference group. Patients in the ACE inhibitor group (n = 49) also tended to have a higher relapse rate (0.29 vs. 0.22, p = 0.357). No differences were observed for the other end points. ***Conclusion:*** In the BEYOND study cohort, a concomitant medication with ARBs or ACE inhibitors did not have a beneficial effect in patients with RRMS treated with interferon beta-1b. As patients appeared to have a higher relapse rate, our results warrant further investigation.

Table 2. Number of patients using ARBs, ACE inhibitors and beta blockers

IFNB-1b (250 + 500 µg)	ARB group (n = 24)	ACE inhibitor group (n = 61)	Beta blocker group (n = 81)
Concomitant medication	valsartan 9 irbesatan 7 olmesartan 5 candesartan 3 eprosartan 1 losartan 1	enalapril 19 lisinopril 19 ramipril 8 benazepril 3 cilazapril 3 moexipril 3 captopril 2 perindopril 2 quinapril 2 trandolapril 1	propranolol 22 metoprolol 20 atenolol 18 bisoprolol 13 timolol 4 carteolol 1 carvedilol 1 celiprolol 1 nadolol 1 sotalol 1
Started medication before study entry	17 (71%)	32[1] (53%)	40[2] (50%)
Mean duration of medication during study, months	19.0	17.1[1]	14.7[2]

The number of drugs may exceed the total numbers of patients because some patients took more than one drug.
[1] Two patients with unknown start/duration of concomitant medication.
[2] One patient with unknown start/duration of concomitant medication.

Table 3. Efficacy outcomes: antihypertensive group (first line) versus matched reference group (second line)

IFNB-1b (250 µg + 500 µg)	ARB group (n = 22)	ACE inhibitor group (n = 49)	Beta blocker group (n = 67)
Annualized relapse rate	0.48 0.23 p = 0.051	0.29 0.22 p = 0.357	0.45 0.33 p = 0.153
Proportion relapse free (year 2)	14 (64) 14 (64) p = 1.0	31 (63) 35 (71) p = 0.518	34 (51) 42 (63) p = 0.222
Confirmed EDSS progression (year 2)	4 (18) 5 (23) p = 1.0	9 (18) 5 (10) p = 0.387	19 (28) 16 (24) p = 0.694
Cumulative number of new T2 lesions (year 2)	2.2 (1, 0–9) 1.8 (0, 0–13) p = 0.519	2.0 (1, 0–16) 2.5 (1, 0–51) p = 0.601	2.1 (1, 0–12) 1.9 (1, 0–12) p = 0.859
Cumulative number of new Gd+lesions (year 2)	0.6 (0, 0–3) 0.3 (0, 0–5) p = 0.057	0.4 (0, 0–4) 0.6 (0, 0–5) p = 0.974	0.2 (0, 0–4) 0.3 (0, 0–4) p = 0.548

Data are mean (median, IQR) and number (%). EDSS = Expanded Disability Status Scale; Gd+lesions = gadolinium-enhancing lesions. Matching for study medication (interferon beta-1b 250 µg, interferon beta-1b 500 µg), sex, age at screening (±2 years), gadolinium-enhancing lesions at baseline (yes/no), number of gadolinium-enhancing lesions at baseline (±3), T2 lesion volume at baseline (±10 cm^3), baseline EDSS (±0.5).

Invited Review

jraas

Journal of the Renin-Angiotensin-Aldosterone System
1–10

DOI: 10.1177/1470320315583582
jra.sagepub.com
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Cerebroprotective effects of RAS inhibitors: Beyond their cardio-renal actions

Jaspreet Kalra[1], Atish Prakash[1,2,3], Puneet Kumar[1] and Abu Bakar Abdul Majeed[2,3]

Abstract

Work on the brain renin–angiotensin system has been explored by various researchers and has led to elucidation of its basic physiologies and behavior, including its role in reabsorption and uptake of body fluid, blood pressure maintenance with angiotensin II being its prominent effector. Currently, this system has been implicated for its newly established effects, which are far beyond its cardio-renal effects accounting for maintenance of cerebral blood flow and cerebroprotection, seizure, in the etiology of Alzheimer's disease, Parkinson's disease, multiple sclerosis, and bipolar disorder. In this review, we have discussed the distribution of angiotensin receptor subtypes in the central nervous system (CNS) together with enzymatic pathways leading to active angiotensin ligands and its interaction with angiotensin receptor 2 (AT2) and Mas receptors. Secondly, the use of angiotensin analogues (angiotensin converting enzyme inhibitors and AT1 and/or AT2 receptor blockers) in the treatment and management of the CNS disorders mentioned above has been discussed.

Multiple sclerosis (MS)/autoimmune demyelination

Inflammation, demyelination, and axon degeneration in the CNS are the major events seen and reported in MS, making it a complex autoimmune disease which is characterized by autoreactive immune cells such as T and B cells. Further, the role of T cell responses has been marked for RAS in an autoimmune disease like of MS.[90] In addition, it has also been noticed that Ang II induced persistent CNS inflammation through upregulation of transforming growth factor (TGF-β) in an experimental autoimmune encephalomyelitis (EAE) mouse model.[91] Ang II receptors are expressed on macrophages and T cells, thus inhibiting ACE which produces Ang II which is seen in EAE, probably by the downregulation of AT1 receptor activation.[90]

Pathogenic condition associated with autoimmune demyelination involves infiltration of macrophages, CD4+ T cells, demyelination in the peripheral white matter of the spinal cord, elevated levels of renin in spleen and spinal cord, and increased expression of AT1aR and AT1bR as well as ACE and ACE2 in peritoneal macrophages and T cells, further causing worsening of the disease.[92] These devastating effects could be suppressed and prevented by the use of ACE inhibitors in the following manner. Firstly, by suppression of autoreactive Th1 and Th17 cells. Secondly, they promote CD4 positive FoxP3 positive Treg in an antigen-specific manner.[93] The renin inhibitor aliskiren and AT1R antagonist losartan have also shown disease ameliorating effects, thus finding a potential therapeutic approach for the treatment of autoimmune demyelination.

Targeting ASIC1 in primary progressive multiple sclerosis: evidence of neuroprotection with amiloride

BRAIN
A JOURNAL OF NEUROLOGY

Tarunya Arun,[1,2,*] Valentina Tomassini,[1,2,3,*] Emilia Sbardella,[1,2,4] Michiel B. de Ruiter,[2,5] Lucy Matthews,[1,2] Maria Isabel Leite,[1] Rose Gelineau-Morel,[6] Ana Cavey,[1] Sandra Vergo,[1,7] Matt Craner,[1,7] Lars Fugger,[1,7] Alex Rovira,[8] Mark Jenkinson[2] and Jacqueline Palace[1]

Neurodegeneration is the main cause for permanent disability in multiple sclerosis. The effect of current immunomodulatory treatments on neurodegeneration is insufficient. Therefore, direct neuroprotection and myeloprotection remain an important therapeutic goal. Targeting acid-sensing ion channel 1 (encoded by the *ASIC1* gene), which contributes to the excessive intracellular accumulation of injurious Na^+ and Ca^{2+} and is over-expressed in acute multiple sclerosis lesions, appears to be a viable strategy to limit cellular injury that is the substrate of neurodegeneration. While blockade of ASIC1 through amiloride, a potassium sparing diuretic that is currently licensed for hypertension and congestive cardiac failure, showed neuroprotective and myeloprotective effects in experimental models of multiple sclerosis, this strategy remains untested in patients with multiple sclerosis. In this translational study, we tested the neuroprotective effects of amiloride in patients with primary progressive multiple sclerosis. First, we assessed ASIC1 expression in chronic brain lesions from post-mortem of patients with progressive multiple sclerosis to identify the target process for neuroprotection. Second, we tested the neuroprotective effect of amiloride in a cohort of 14 patients with primary progressive multiple sclerosis using magnetic resonance imaging markers of neurodegeneration as outcome measures of neuroprotection. Patients with primary progressive multiple sclerosis underwent serial magnetic resonance imaging scans before (pretreatment phase) and during (treatment phase) amiloride treatment for a period of 3 years. Whole-brain volume and tissue integrity were measured with high-resolution T_1-weighted and diffusion tensor imaging. In chronic brain lesions of patients with progressive multiple sclerosis, we demonstrate an increased expression of ASIC1 in axons and an association with injury markers within chronic inactive lesions. In patients with primary progressive multiple sclerosis, we observed a significant reduction in normalized annual rate of whole-brain volume during the treatment phase, compared with the pretreatment phase ($P = 0.018$, corrected). Consistent with this reduction, we showed that changes in diffusion indices of tissue damage within major clinically relevant white matter (corpus callosum and corticospinal tract) and deep grey matter (thalamus) structures were significantly reduced during the treatment phase ($P = 0.02$, corrected). Our results extend evidence of the contribution of ASIC1 to neurodegeneration in multiple sclerosis and suggest that amiloride may exert neuroprotective effects in patients with progressive multiple sclerosis. This pilot study is the first translational study on neuroprotection targeting ASIC1 and supports future randomized controlled trials measuring neuroprotection with amiloride in patients with multiple sclerosis.

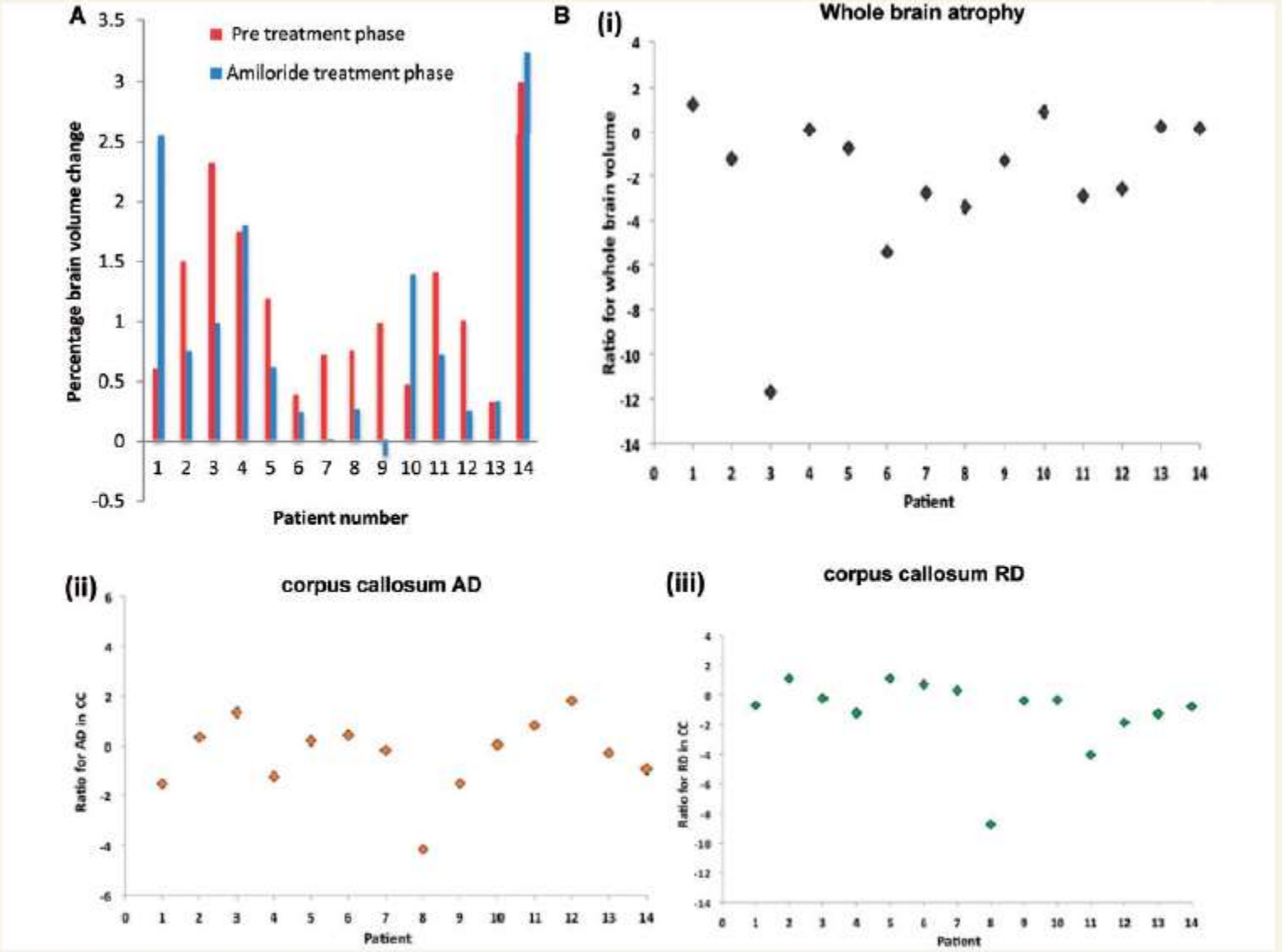
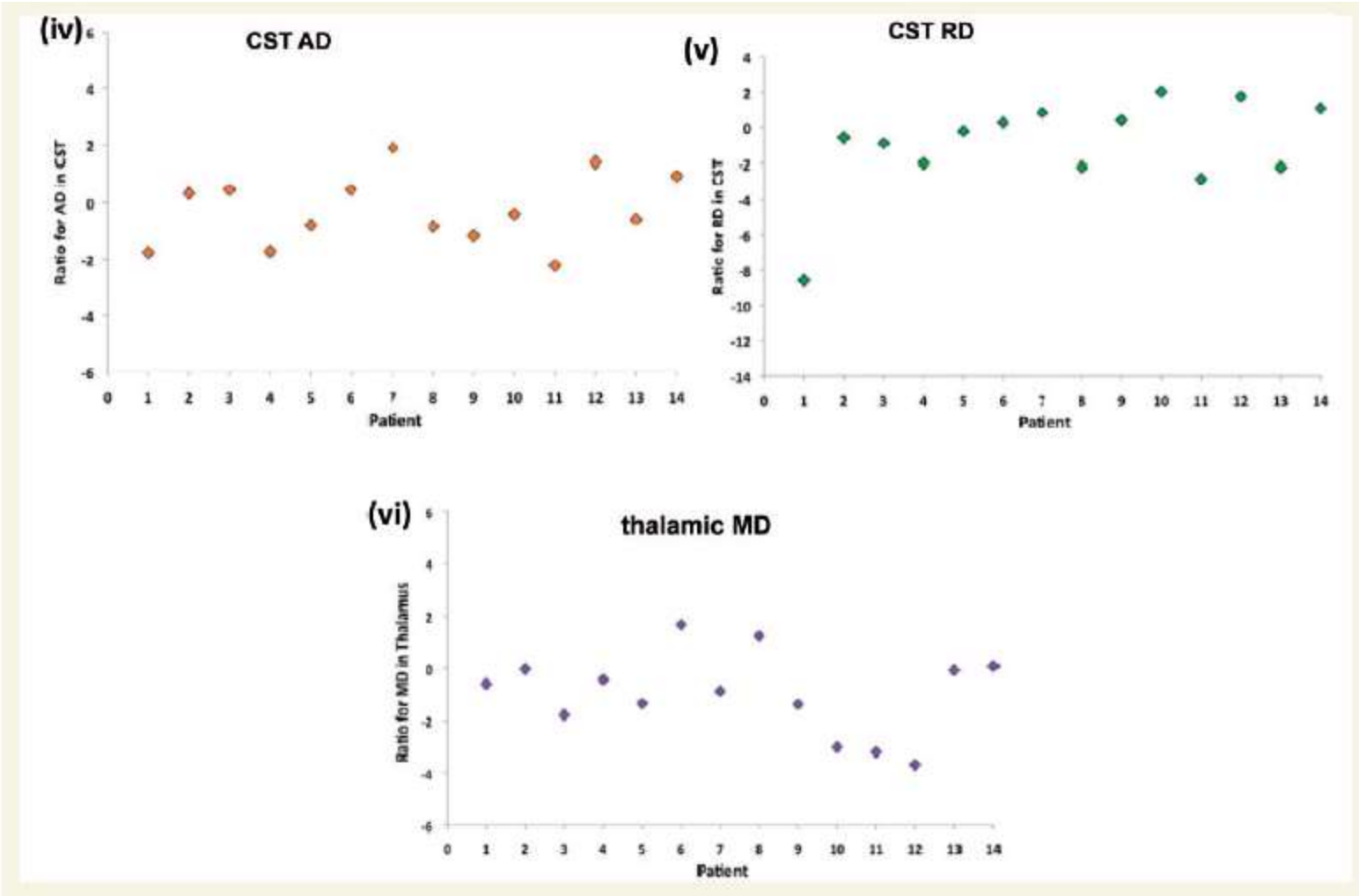
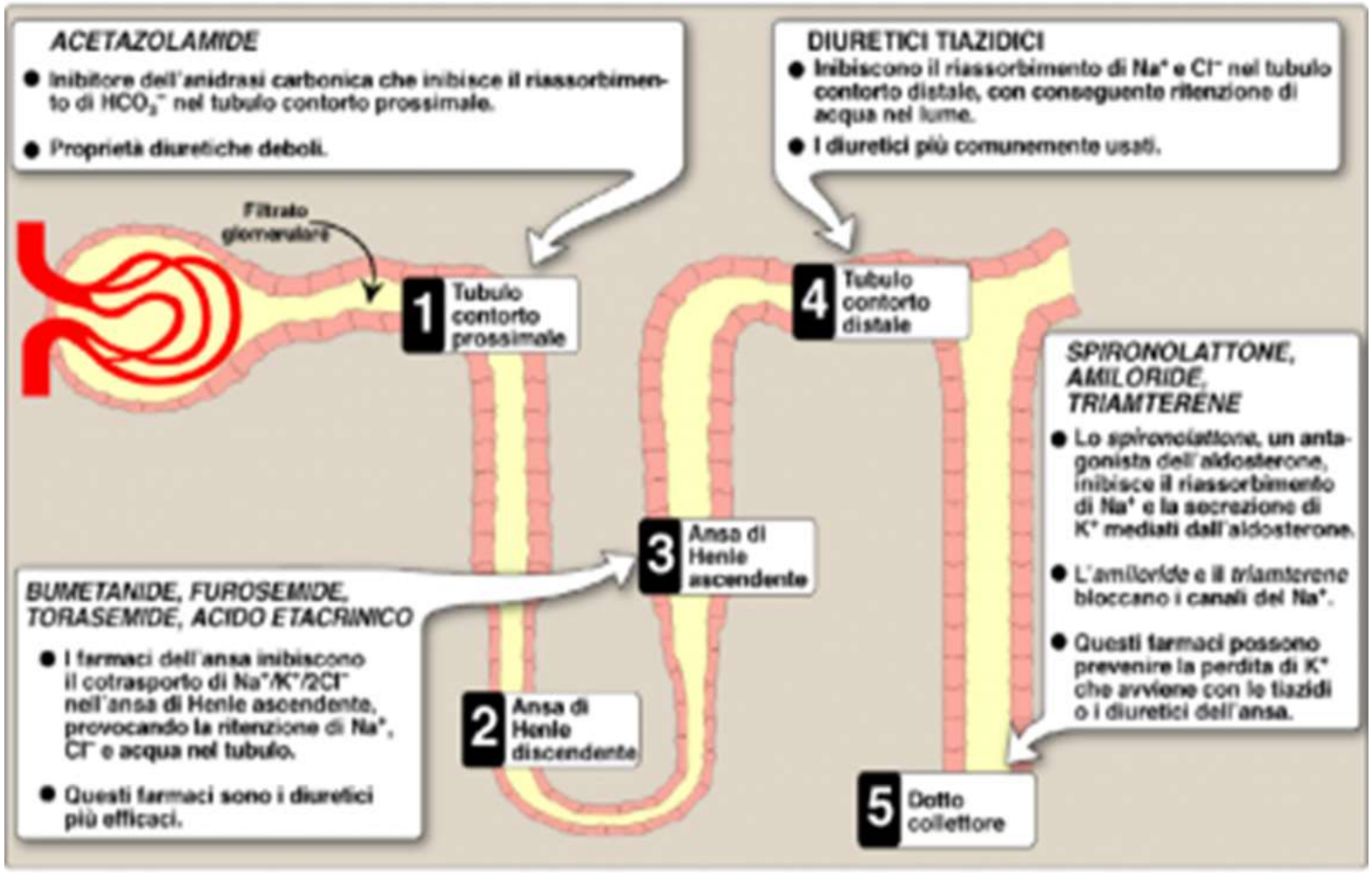


Figure 5 (**A**) Pretreatment and post-treatment atrophy rates for individual patients. (**B**) Rate of change on treatment minus rate for pretreatment, adjusted for variability (i.e. a ratio formed by dividing the difference in rates by the SD of this difference). Positive values indicate faster rates of changes during the amiloride treatment phase compared with the pretreatment phase, whereas negative values indicate slower rates of change in the amiloride treatment phase compared with the pretreatment phase: (**i**) brain atrophy, (**ii**) axial diffusivity (AD) in corpus callosum (CC), (**iii**) radial diffusivity (RD) in corpus callosum, (**iv**) axial diffusivity in corticospinal tract (CST), (**v**) radial diffusivity in corticospinal tract and (**vi**) mean diffusivity of thalamus. Before statistical testing, an average of the diffusion measures was produced across homologous regions of the two hemispheres.


(iv)
CST AD
Ratio for AD in CST
Patient
(v)
CST RD
Ratio for RD in CST
Patient
(vi)
thalamic MD
Ratio for MD in Thalamus
Patient


ACETAZOLAMIDE
Inibitore dell'anidrasi carbonica che inibisce il riassorbimento di HCO_3^- nel tubulo contorto prossimale.
Proprietà diuretiche deboli.
DIURETICI TIAZIDICI
Inibiscono il riassorbimento di Na^+ e Cl^- nel tubulo contorto distale, con conseguente ritenzione di acqua nel lume.
I diuretici più comunemente usati.
Filtrato glomerulare
1 Tubulo contorto prossimale
2 Ansa di Henle discendente
3 Ansa di Henle ascendente
4 Tubulo contorto distale
5 Dotto collettore
BUMETANIDE, FUROSEMIDE, TORASEMIDE, ACIDO ETACRINICO
I farmaci dell'ansa inibiscono il cotrasporto di $Na^+/K^+/2Cl^-$ nell'ansa di Henle ascendente, provocando la ritenzione di Na^+, Cl^- e acqua nel tubulo.
Questi farmaci sono i diuretici più efficaci.
SPIRONOLATTONE, AMILORIDE, TRIAMTERENE
Lo spironolattone, un antagonista dell'aldosterone, inibisce il riassorbimento di Na^+ e la secrezione di K^+ mediati dall'aldosterone.
L'amiloride e il triamterene bloccano i canali del Na^+.
Questi farmaci possono prevenire la perdita di K^+ che avviene con le tiazidi o i diuretici dell'ansa.

CNS Drugs (2015) 29:277–291
DOI 10.1007/s40263-015-0239-x

SYSTEMATIC REVIEW

Statin Treatment in Multiple Sclerosis: A Systematic Review and Meta-Analysis

Gorm Pihl-Jensen · Anna Tsakiri · Jette Lautrup Frederiksen

Abstract

Background Multiple sclerosis (MS) is a chronic inflammatory disease that leads to progressive disability. Statins [hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors] are widely prescribed drugs in hypercholesterolemia. They exert immunomodulatory and neurotrophic effects and are attractive candidates for MS treatment due to reliable safety profiles and favorable costs. Studies of statins in a murine MS model and in open-label trials in MS have shown decreased disease severity.

Objective Our objective was to assess current evidence to support statin treatment in MS and clinically isolated syndrome (CIS).

Methods We conducted a systematic literature review of EMBASE, PubMed, and CINAHL databases, clinical trials registries, and unpublished conference meeting abstracts as well as reference lists between 1 and 8 June 2014 and repeated it on 1 December 2014. Randomized controlled trials (RCTs) of statins, in any form or dosage, as monotherapy or add-on to established therapy in relapsing-remitting MS (RRMS), progressive MS, and CIS were included. Data were extracted using pre-defined fields to measure study quality. Meta-analysis was performed with regards to pre-defined outcome measures of relapse activity, magnetic resonance imaging (MRI) activity, Expanded Disability Status Scale (EDSS) progression, and adverse events using a fixed-effects model due to low heterogeneity between studies.

Results Eight trials were included in the review [five of statin add-on to interferon (IFN)-β treatment in RRMS, one of statin monotherapy in CIS, one of statin monotherapy in optic neuritis (ON)/CIS, and one of statin monotherapy in secondary progressive MS (SPMS)]. Three trials with eligible characteristics had not been published in peer-reviewed journals and were therefore not included. Due to the low number of trials in CIS and SPMS, meta-analysis of primary outcomes was only performed for RRMS studies. Meta-analysis showed no significant effect of statin add-on to IFNβ therapy. Indeed, a trend towards an increase in disease activity was shown in the statin group with regards to new T2 lesions, proportion of patients with relapse, and whole brain atrophy but not for EDSS progression. In SPMS, statin monotherapy showed significant reduction in brain atrophy and disability progression but no effect on relapse rate. In CIS, a phase II trial showed no difference in relapse activity, MRI activity or risk of MS between statin monotherapy and placebo. In acute ON, statin monotherapy produced better visual outcome but no difference in relapse activity, MRI activity, or risk of MS.

Conclusions The pleiotropic effects and effects in the murine model of MS could not be converted to a proven effect in relapsing MS and hence statin therapy either as a monotherapy or in combination with IFNβ treatment for RRMS, and statin monotherapy for CIS cannot at present be recommended. However, indications are that statins may be beneficial in SPMS. The benefit thereof and

Electronic supplementary material The online version of this article (doi:10.1007/s40263-015-0239-x) contains supplementary material, which is available to authorized users.

G. Pihl-Jensen (✉) · A. Tsakiri · J. L. Frederiksen
Clinic of Optic Neuritis and Clinic of Multiple Sclerosis, Neurological Department, Glostrup Hospital, University of Copenhagen, Nordre Ringvej 57, 2600 Glostrup, Denmark
e-mail: gorm.pihl-jensen@regionh.dk

A. Tsakiri
e-mail: ants@dadlnet.dk

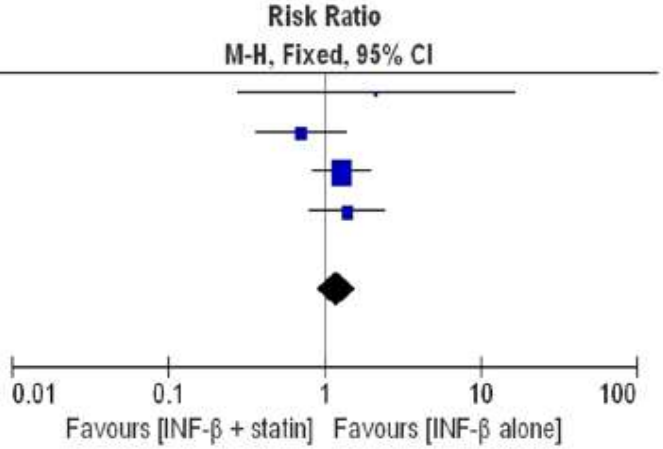
J. L. Frederiksen
e-mail: jette.lautrup.frederiksen.battistini@regionh.dk

(a) Proportion of patients experiencing relapse during the study

Study or Subgroup	INF-β and statin Events	Total	INF-β alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Birnbaum et al.	4	17	1	9	2.3%	2.12 [0.28, 16.24]	2008
Lanzillo et al.	8	21	13	24	21.7%	0.70 [0.36, 1.36]	2010
Sørensen et al.	37	151	30	156	52.7%	1.27 [0.83, 1.95]	2011
Kamm et al.	18	38	13	38	23.2%	1.38 [0.80, 2.41]	2012
Total (95% CI)		**227**		**227**	**100.0%**	**1.20 [0.89, 1.61]**	
Total events	67		57				

Heterogeneity: $Chi^2 = 3.16$, df = 3 (P = 0.37); $I^2 = 5\%$

Test for overall effect: Z = 1.17 (P = 0.24)

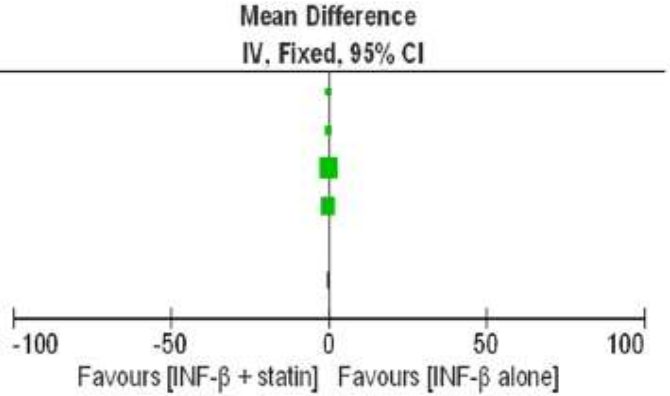


(b) Change in EDSS during the study

Study or Subgroup	INF-β and statin Mean	SD	Total	INF-β alone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
Lanzillo et al.	0.2	1.1	19	0.4	1.1	19	7.9%	-0.20 [-0.90, 0.50]	2010
Togha et al.	-0.2	1.35	42	0.1	1.26	38	11.8%	-0.30 [-0.87, 0.27]	2010
Sørensen et al.	0.17	1.14	137	0.14	1.3	133	45.2%	0.03 [-0.26, 0.32]	2011
Kamm et al.	0.03	0.9	37	0.17	0.5	38	35.2%	-0.14 [-0.47, 0.19]	2012
Total (95% CI)			**235**			**228**	**100.0%**	**-0.09 [-0.28, 0.11]**	

Heterogeneity: $Chi^2 = 1.35$, df = 3 (P = 0.72); $I^2 = 0\%$

Test for overall effect: Z = 0.87 (P = 0.39)



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DOI 10.1007/s40263-015-0239-x

SYSTEMATIC REVIEW

Statin Treatment in Multiple Sclerosis: A Systematic Review and Meta-Analysis

Gorm Pihl-Jensen · Anna Tsakiri · Jette Lautrup Frederiksen

Key Points

Statins are attractive candidates for treatment of multiple sclerosis (MS) due to reliable safety profiles, low costs, and established immunomodulatory and neurotrophic effects as well as effects in a murine model of MS.

Monotherapy in relapsing MS has shown subtle signs of effect, but supplementation to established interferon-β therapy is without significant benefit.

Recent study in secondary progressive MS showed decreased brain atrophy and effect on disability on statin monotherapy. Further studies are required to confirm this finding.

Published in final edited form as:
Arch Neurol. 2012 October ; 69(10): 1303–1309. doi:10.1001/archneurol.2012.465.

Inhibition of Interferon-beta Responses in Multiple Sclerosis Immune Cells Associated With High-Dose Statins

Dr. Xuan Feng, PhD, **Ms. Diana Han, BA**, **Mr. Bharat K. Kilaru, BA**, **Ms. Beverly S. Franek, BS**, **Dr. Timothy B. Niewold, MD**, and **Dr. Anthony T. Reder, MD**
Departments of Neurology (Drs Feng and Reder, Ms Han, and Mr Kilaru) and Medicine (Ms Franek and Dr Niewold), The University of Chicago, Chicago, Illinois

Abstract

Objective—To determine whether statins affect type 1 interferon responses in relapsing-remitting multiple sclerosis (RRMS).

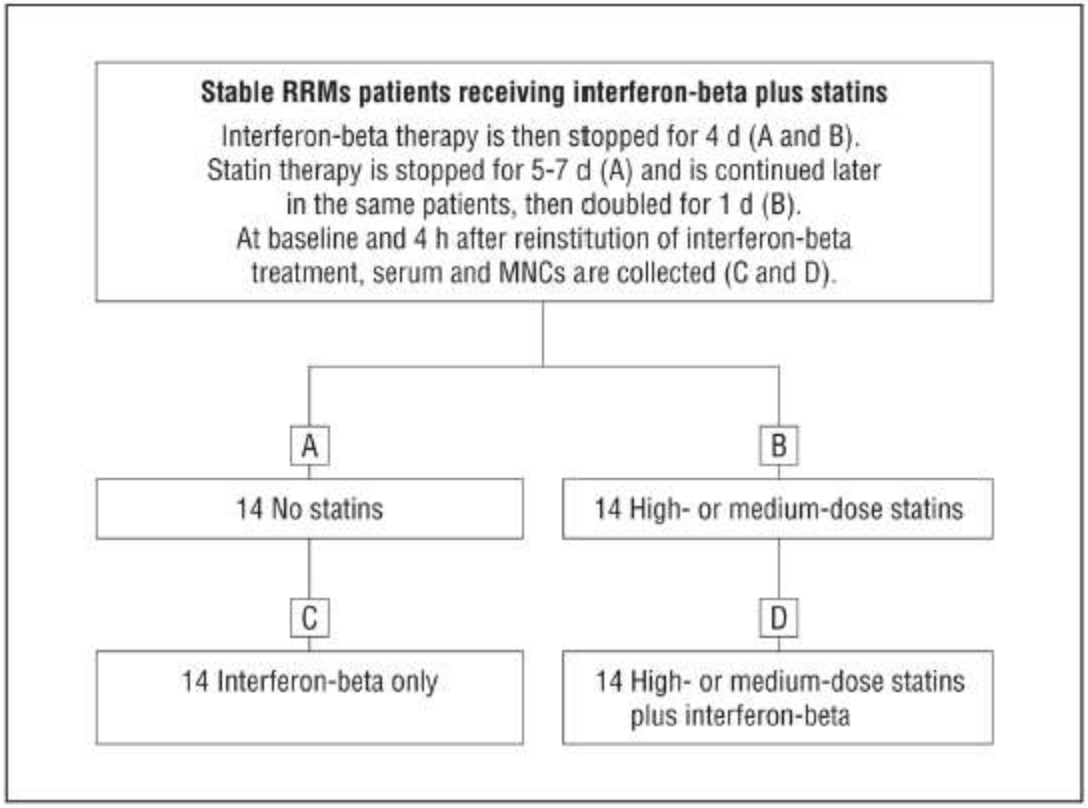
Design—Study effects of atorvastatin on type 1 interferon responses in Jurkat cells, mononuclear cells (MNCs) from therapy-naive patients with RRMS in vitro, and MNCs from interferon-treated RRMS patients in vivo in 4 conditions: no drug, statin only, interferon-beta only, and statin added on to interferon-beta therapy.

Patients—The study examined clinically stable patients with RRMS: 21 therapy-naive patients and 14 patients receiving interferon-beta with a statin.

Interventions—Statin effects on in vitro and in vivo interferon-beta–induced STAT1 transcription factor activation, expression of interferon-stimulated proteins in MNCs, and serum type 1 interferon activity.

Results—In vitro, atorvastatin dose dependently inhibited expression of interferon-stimulated P-Y-STAT1 by 44% ($P < .001$), interferon regulatory factor 1 protein by 30% ($P = .006$), and myxovirus resistance 1 protein by 32% ($P = .004$) compared with no-statin control in MNCs from therapy-naive RRMS patients. In vivo, 9 of 10 patients who received high-dose statins (80 mg) had a significant reduction in interferon-beta therapy–induced serum interferon-α/β activity, whereas only 2 of 4 patients who received medium-dose statins (40 mg) had reductions. High-dose add-on statin therapy significantly blocked interferon-beta function, with less P-Y-STAT1 transcription factor activation, and reduced myxovirus resistance 1 protein and viperin protein production. Medium doses of statins did not change STAT1 activation.

Conclusions—High-dose add-on statin therapy significantly reduces interferon-beta function and type 1 interferon responses in RRMS patients. These data provide a putative mechanism for how statins could counteract the beneficial effects of interferon-beta and worsen disease.


Stable RRMs patients receiving interferon-beta plus statins
Interferon-beta therapy is then stopped for 4 d (A and B).
Statin therapy is stopped for 5-7 d (A) and is continued later in the same patients, then doubled for 1 d (B).
At baseline and 4 h after reinstitution of interferon-beta treatment, serum and MNCs are collected (C and D).
A
B
14 No statins
14 High- or medium-dose statins
C
D
14 Interferon-beta only
14 High- or medium-dose statins plus interferon-beta

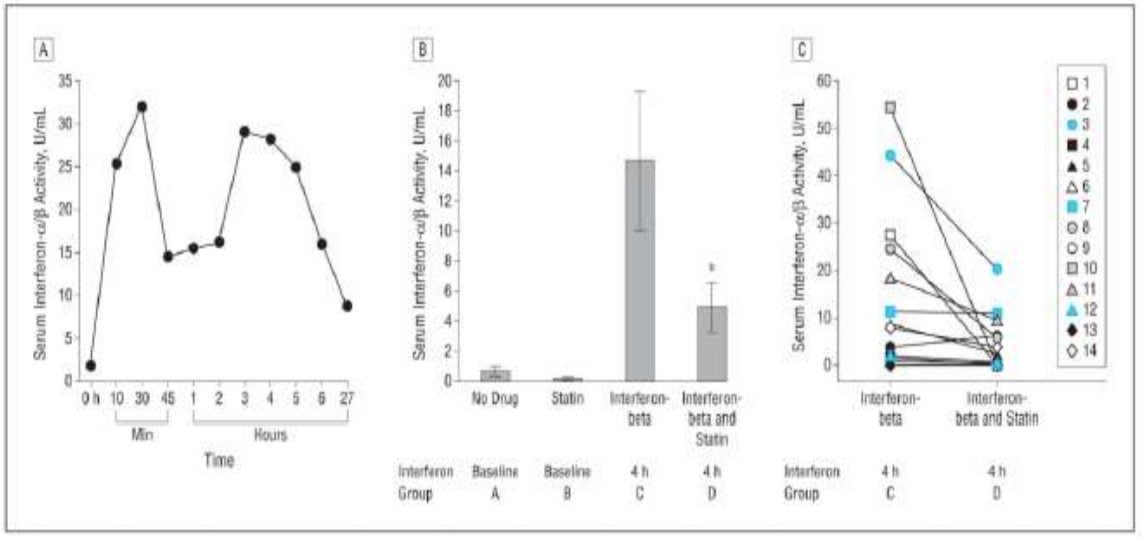


Figure 3.

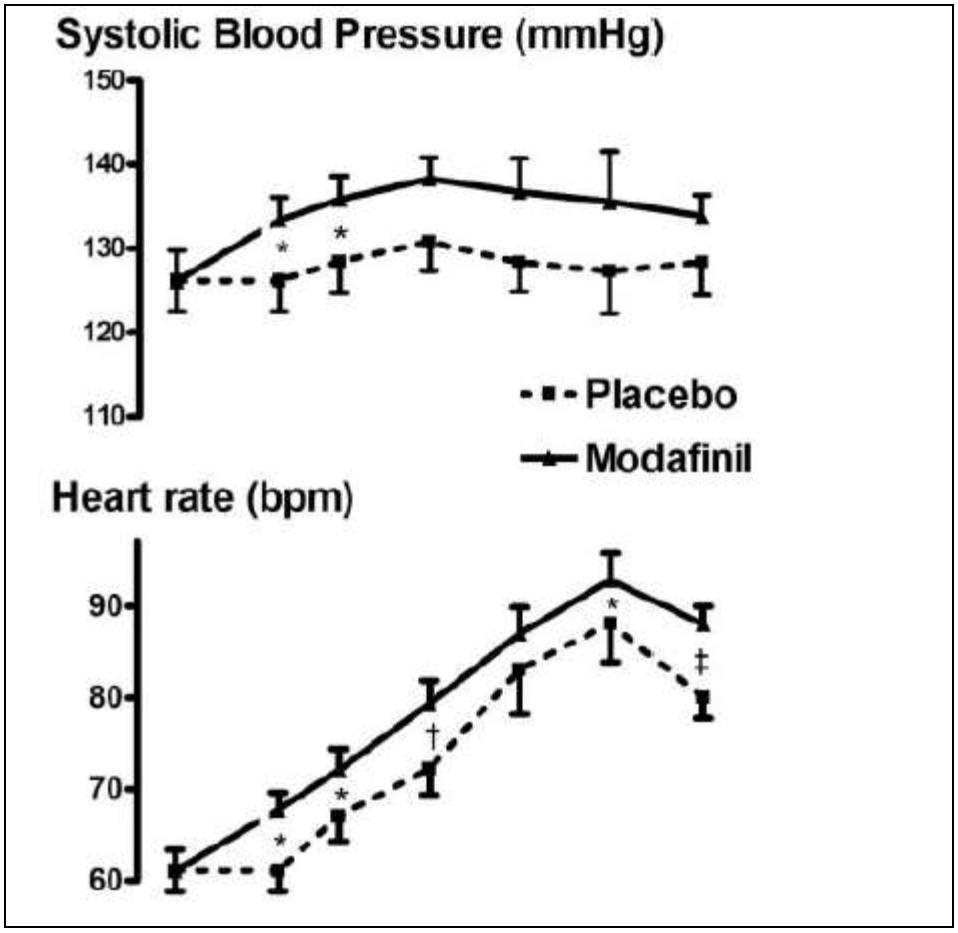
Statins reduce interferon-beta therapy induction of serum type 1 interferon activity in 14 stable patients with relapsing-remitting multiple sclerosis. A, In vivo Rebif kinetics after a 3-day washout. B and C, Statin add-on therapy blocks interferon-beta therapy induction of serum interferon-α/β activity in 14 patients with relapsing-remitting multiple sclerosis. Serum samples were obtained at 8 am after statin washout or long-term statin alone and then exactly 4 hours after interferon-beta injections or high-dose statins plus 4 hours of interferon-beta therapy. *P <.001 vs interferon alone (paired t test). Error bars indicate SEM.

Modafinil Elicits Sympathomedullary Activation

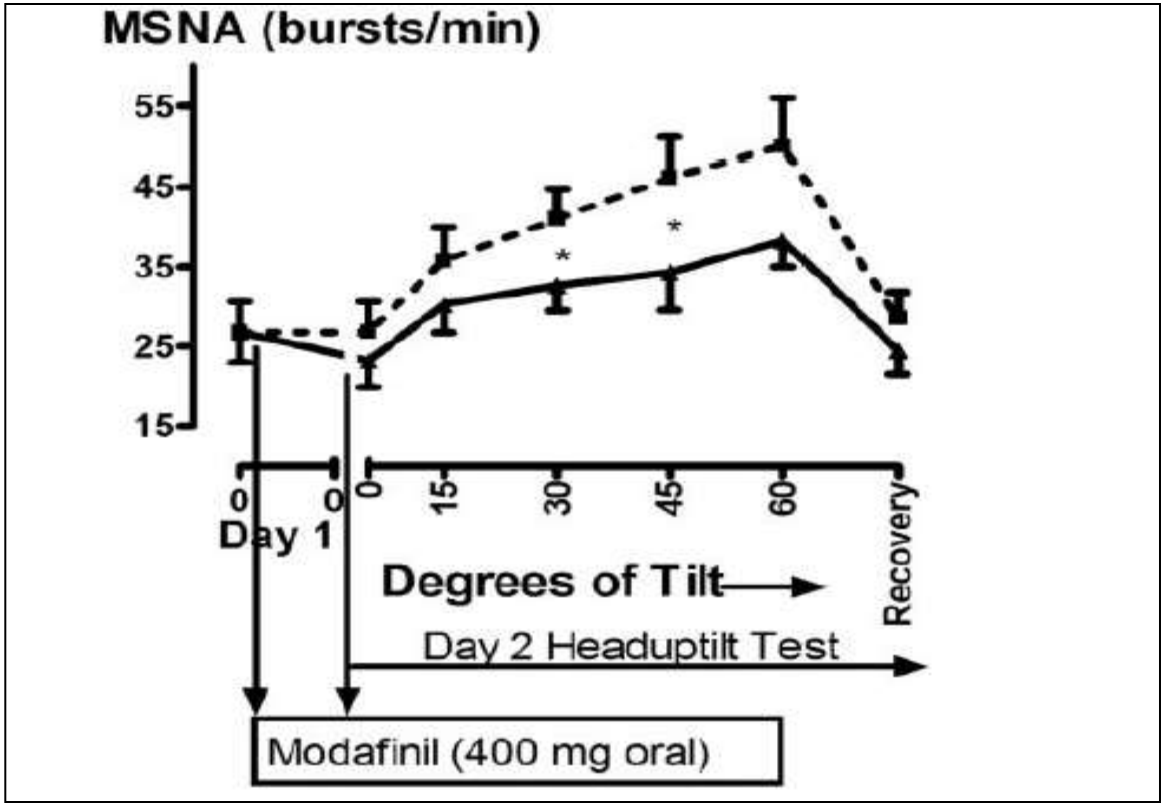
Indu Taneja, Andre Diedrich, Bonnie K. Black, Daniel W. Byrne,
Sachin Y. Paranjape, David Robertson

Abstract—The autonomic effects of modafinil (Provigil), a psychostimulant widely used to attenuate fatigue and promote wakefulness, are currently unexplored. We assessed the effect of modafinil on autonomic nervous system. We compared oral modafinil (400 mg×1) versus placebo in 12 healthy hospitalized normal subjects in a randomized double-blind, placebo-controlled cross-over study for 3 days each with subjects in 150 mEq sodium, 70 mEq potassium balance at the Vanderbilt General Clinical Research Center. Modafinil increased resting heart rate (9.2±2.0 bpm; mean [±SE]; 95% confidence interval [CI], 4.7 to 13.6; $P=0.001$), resting systolic blood pressure (7.3±3.2 mm Hg; 95% CI, 0.2 to 14.4; $P=0.044$), and resting diastolic blood pressure (5.3±1.7 mm Hg; 95% CI, 1.4 to 9.1 mm Hg; $P<0.012$). Modafinil elicited a 42% higher orthostatic increase in plasma norepinephrine (0.8±0.3 nmol/L; 95% CI, 0.2 to 1.3; $P=0.01$), and caused a 33% increase in urine norepinephrine (5.1±1.1 nmol/L creatinine per day; 95% CI, 2.7 to 7.4, $P=0.001$), and an 81% increase in urine epinephrine (1.3±0.2 nmol/L creatinine per day; 95% CI, 1 to 2; $P<0.001$). The peroneal microneurographic sympathetic activity was attenuated by modafinil during orthostatic tilt ($P<0.001$). α1-Adrenoreceptor function was maintained. Modafinil substantially perturbs autonomic cardiovascular regulation by increase in heart rate and blood pressure. Autonomic changes of this magnitude encourage caution in use of modafinil in patients with cardiovascular disease. (***Hypertension*. 2005;45:612-618.**)

Key Words: blood pressure ■ catecholamines ■ heart rate ■ norepinephrine ■ baroreflex


Systolic Blood Pressure (mmHg)
150
140
130
120
110
Placebo
Modafinil
Heart rate (bpm)
90
80
70
60

The peroneal microneurographic sympathetic activity



Journal of Autonomic Pharmacology, 19, 347–352

Modification of cardiovascular responses to spinal $GABA_B$ receptor stimulation by cAMP and by K_{ATP} channel blockade in anaesthetized rats

H. C. Koh[1], I. C. Shin[1], J. H. Ha[1], D. J. Paik[2], J. S. Kang[1] & C. H. Lee[1]

[1]Department of Pharmacology; [2]Department of Anatomy, College of Medicine, Hanyang University, 17 Haengdang-Dong, Sungdong-Gu, Seoul 133-791, South Korea

Correspondence:
H. C. Koh

Summary

1 Intrathecal (i.t.) injection of baclofen (30, 60 and 100 nmol), a $GABA_B$ receptor agonist, produced a dose-dependent decrease in blood pressure (BP) and heart rate (HR).
2 Pretreatment with 5-aminovaleric acid (50 nmol), a $GABA_B$ receptor antagonist, blocked the depressor and bradycardic effects of baclofen (100 nmol).
3 Pretreatment with 8-bromo-cAMP (10 nmol), a cAMP analogue, attenuated the depressor and bradycardic effects of baclofen (100 nmol), but not with 8-bromo-cGMP (10 nmol), a cGMP analogue.
4 In addition, pretreatment with glipizide (20 nmol), an ATP-sensitive K^+ channel (K_{ATP}) blocker, attenuated the depressor and bradycardic effects of baclofen (100 nmol).
5 These results suggest that $GABA_B$ receptors in the spinal cord have an inhibitory role in the central cardiovascular regulation and that these depressive and bradycardic actions are modified by cAMP and by K_{ATP} channel blockade.

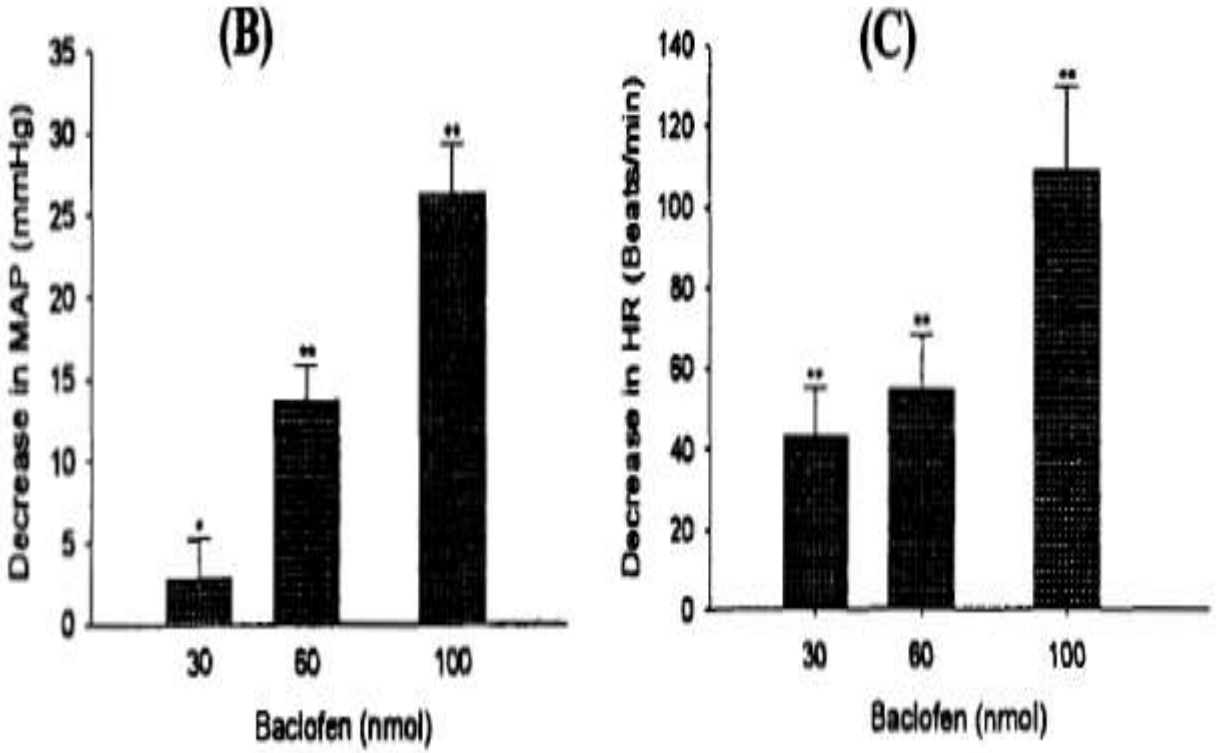


Figure 1 Decrease of blood pressure (BP) and heart rate (HR) induced by i.t. injection of baclofen. (A) Representative tracings depicting the changes of BP and HR following microinjection of baclofen (100 nmol i.t.). (B) Dose-dependent decrease of MAP by i.t. injection of baclofen (30, 60, 100 nmol). (C) Dose-dependent decrease of HR by i.t. injection of baclofen (30, 60, 100 nmol). Results represent mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$, compared to baseline MAP and HR.

La terapia “disease modyfing”

Ha l’obiettivo di modificare la storia naturale della malattia

Le terapie oggi disponibili agiscono riducendo significativamente l’attività di malattia e/o ritardando la progressione della disabilità neurologica che essa comporta

ORIGINAL RESEARCH ARTICLE

Cardiovascular Therapeutics

Disease Modifying Therapies Modulate Cardiovascular Risk Factors in Patients with Multiple Sclerosis

Zohara Sternberg,[1] Christopher Leung,[1] Daniel Sternberg,[1] Jinhee Yu[2] & David Hojnacki[1]

1 Department of Neurology, Stroke Center, Buffalo Medical Center, Buffalo, NY, USA
2 Department of Biostatistics, University of Buffalo, Buffalo, NY, USA

Keywords
Blood pressure; Disease modifying therapy; Disease severity; Lipid profile; Multiple sclerosis; Plasma glucose.

Correspondence
Zohara Sternberg PhD, Assistant Professor of Neurology, Buffalo Medical Center, Buffalo, NY 14203, USA.
Tel.: +1-716-859-4235;
Fax: +1-716-859-2430, +1-716-859-7573;
E-mail: zs2@buffalo.edu

doi: 10.1111/1755-5922.12049

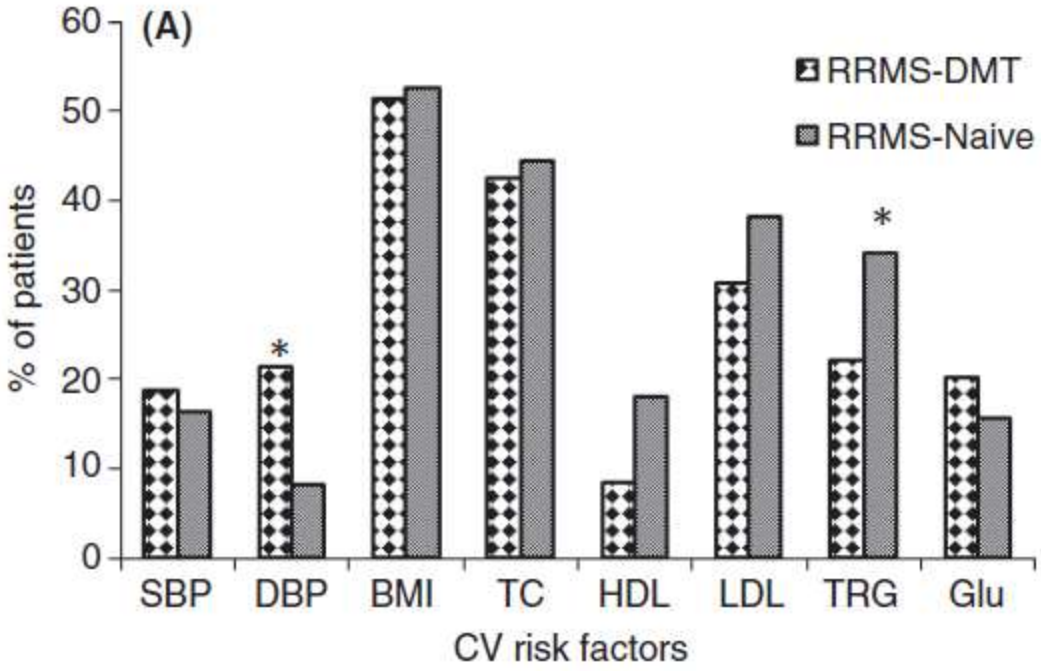
SUMMARY

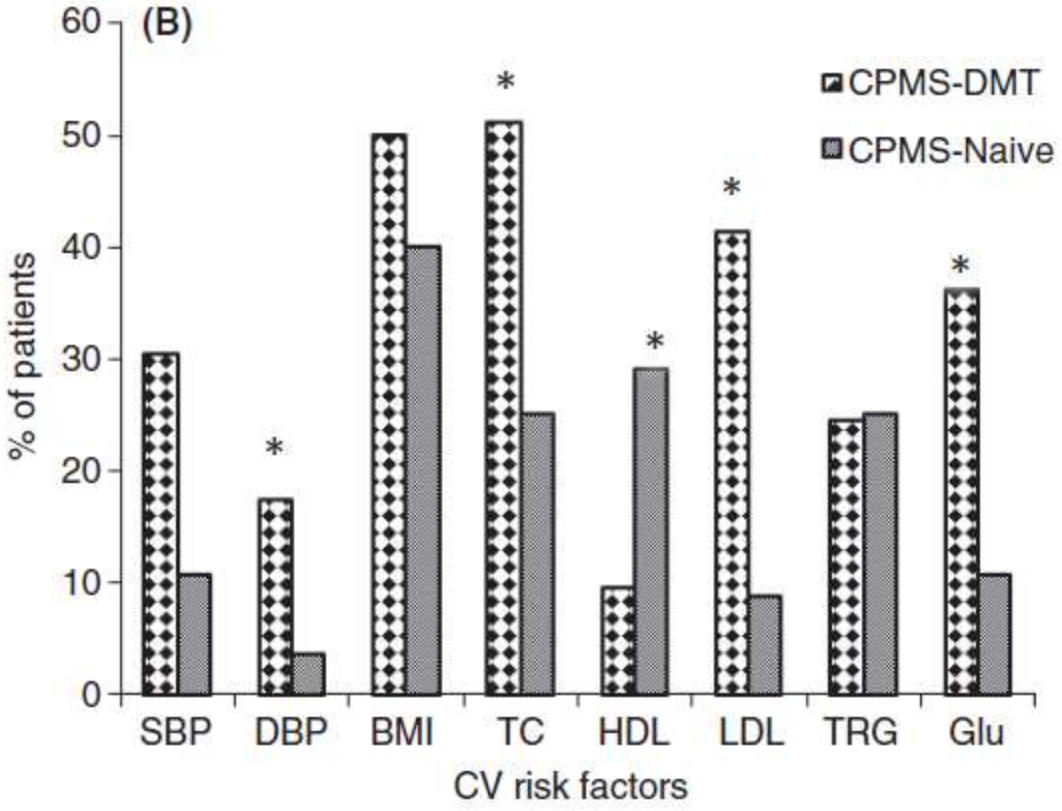
Objectives: This retrospective study aimed to determine (1) the association between the use of three major disease modifying therapies (DMTs) (Interferon-beta [IFN-β], Glatiramer acetate [GA], Natalizumab [NTZ]) and cardiovascular (CV) risk factors in multiple sclerosis (MS) patients, and (2) the association between the use of CV drugs (antihypertensive, hypolipidemic, and antiplatelets) and other drugs acting on the CV system (antispastics/anticonvulsants/anxyolitics, antidepressants/stimulants), and MS disease severity. **Methods:** The charts of 188 patients with MS, who were taking one of the three DMTs, and 110 patients, who were naïve to these drugs, were retrospectively reviewed. The obtained data included height and weight, fasting lipid profiles, plasma glucose, systolic and diastolic BP, smoking habit, list of medications, and indicators of MS disease severity. **Results:** The use of DMTs was associated with higher diastolic BP readings, as well as higher plasma glucose and HDL-C plasma levels. In addition, there was an association between CV risk factors and the type of DMTs. When compared to DMT-naïve patients with MS, the use of IFN-β and GA was associated with higher CV risk factors, whereas the use of NTZ was associated with lower CV risk factors. In DMT-naïve patients, the use of CV and related drugs was associated with higher Extended Disability Status Scale (EDSS) and higher MS Severity Scale (MSSS). **Conclusion:** There is an association between higher CV risk factors and the use of DMTs. Furthermore, CV and related drugs have the potential for modulating MS disease severity.

Table 2 The association between CV risk factors and the use of DMTs

CV Risk Factors	DMT-users (n = 188)	DMT-naïve (n = 110)	*P*-value
Systolic BP (%> 140 mmHg)	125.2 ± 17.1 (22.2)	122.2 ± 18.7 (14.4)	0.12
Diastolic BP (% >90 mmHg)	79.129 ± 11.8 (20.2)	74.9 ± 9.4 (5.3)	0.03
BMI (% >25 kg/m^2)	26.4 ± 5.7 (51.6)	25.8 ± 5.4 (47.2)	0.23
TC (% >200 mg/dL)	198.27 ± 40.0 (44.8)	189.4 ± 43.7 (33.8)	0.33
HDL-C (% <40 mg/dL)	56.0 ± 13.7 (7.0)	52.9 ± 15.8 (18.6)	0.01
LDL-C (% >130 mg/dL)	118.7 ± 33.5 (33.7)	111.0 ± 33.1 (26.3)	0.47
TRG (% >150 mg/dL)	117.1 ± 62.9 (22.7)	139.0 ± 89.1 (31.0)	0.23
Glucose (% >100 mg/dL)	94.2 ± 20.7 (24.5)	89.8 ± 15.0 (13.8)	0.02
Smoking (current or former), %	33.8	34.7	0.90

BP, blood pressure; BMI, body mass index; CV, cardiovascular; DMT, disease modifying therapy; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TRG, triglyceride. $P \leq 0.05$ is statistically significant and are based on percentages.


(A)
RRMS-DMT
RRMS-Naive
% of patients
60
50
40
30
20
10
0
*
*
SBP
DBP
BMI
TC
HDL
LDL
TRG
Glu
CV risk factors


(B)
60
50
40
30
20
10
0
% of patients
CPMS-DMT
CPMS-Naive
*
*
*
*
*
SBP
DBP
BMI
TC
HDL
LDL
TRG
Glu
CV risk factors

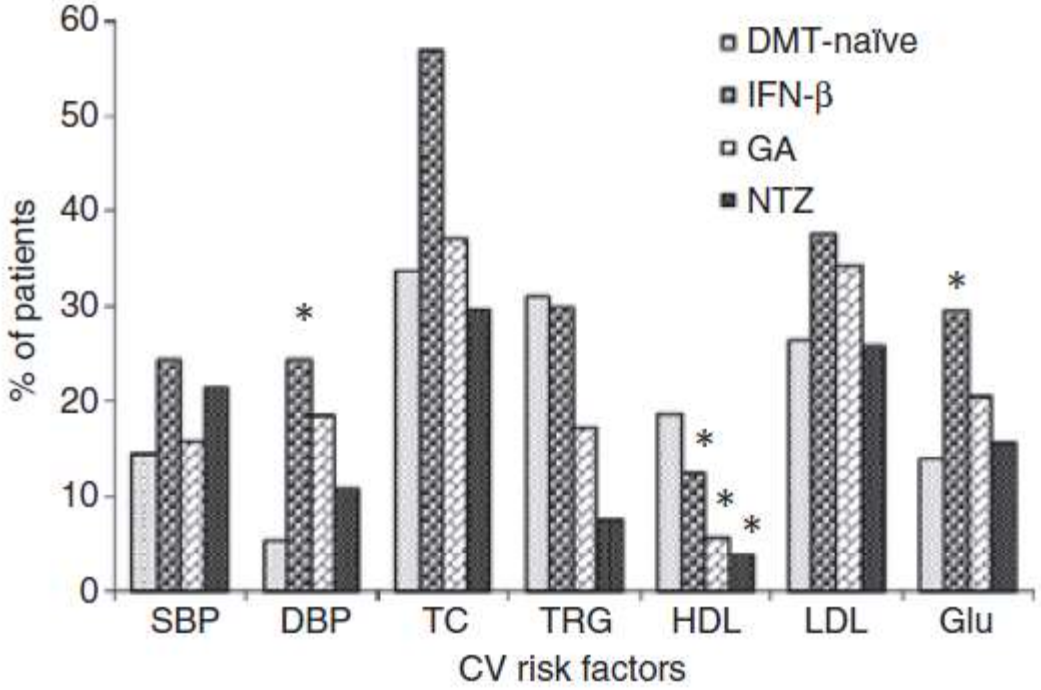


Figure 2 The association between the type of DMT and CV risk factors in MS patients. The Figure presents the percentages of MS patients, who were naïve to DMTs or were treated with one of the three DMTs, and who showed CV risk factors above the normal ranges. IFN, interferon; GA, Glatiramer acetate; NTZ, Natalizumab.

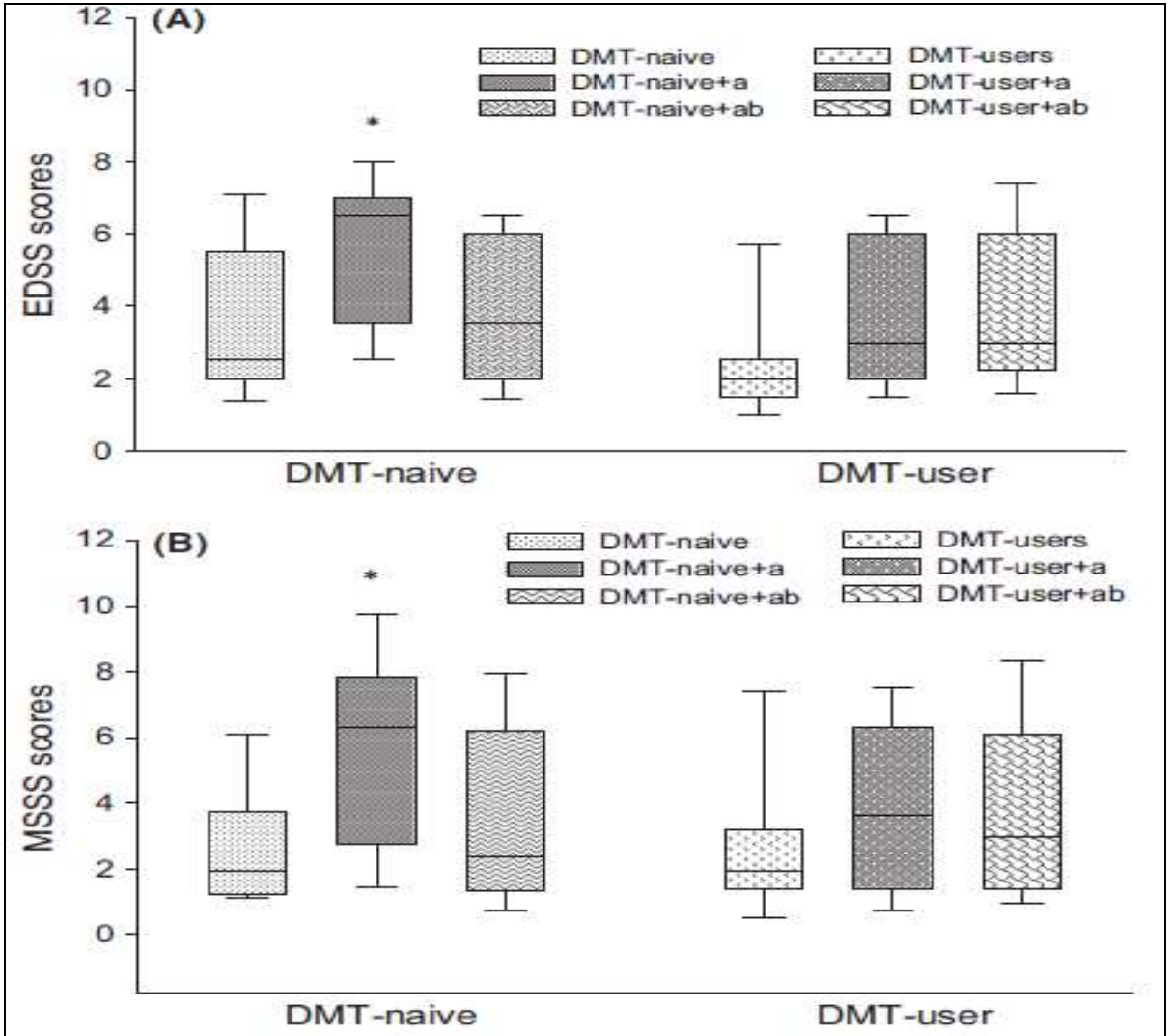


Figure 3 The association between MS disease severity (EDSS [Figure 3A], MSSS [Figure 3B]), and the use of CV and related drugs, in DMT-naïve patients and DMT-users. EDSS, expanded disability status scale; MSSS, multiple sclerosis severity scale. a: antihypertensives + hypolipidemics + antiplatelets + antispastics/anticonvulsants/anxiolytics. ab: stimulants (antidepressants + modafinil) + antihypertensives + hypolipidemics + antiplatelets + antispastics/anticonvulsants/anxiolytics.

Psychoneuroendocrinology. **2002** Nov;27(8):881-92.

Acute interferon beta-1b administration alters hypothalamic-pituitary-adrenal axis activity, plasma cytokines and leukocyte distribution in healthy subjects.

Goebel MU[1], Baase J, Pithan V, Exton M, Saller B, Schedlowski M, Limmroth V.

Author information

Abstract

It has been suggested that the immune-endocrine communication plays an important role in development and progression of multiple sclerosis (MS). Interferon beta (IFN beta-1b) treatment is the therapy of choice in patients suffering from relapsing remitting or secondary chronic progressive multiple sclerosis. While typical adverse events of IFN beta-1b treatment such as flu-like symptoms or fatigue are well studied, little is known about the acute changes in the immune and neuroendocrine system. Therefore, we analyzed the short-term effects of IFN beta-1b on cortisol, epinephrine, norepinephrine, prolactin and growth hormone (GH) plasma levels before and 4, 8 and 24 h after IFN beta-1b administration in healthy subjects. Moreover, we determined heart rate, blood pressure, body temperature, leukocyte and lymphocyte subsets and plasma levels of interleukin (IL)-1 beta, IL-6, IL-10 and tumor necrosis factor (TNF)-alpha. IFN beta-1b led to an increase in body temperature and heart rate, and in parallel, elevated cortisol, prolactin and GH plasma levels at 4 and 8 h after IFN beta-1b injection. There were no significant alterations in blood pressure, norepinephrine or epinephrine plasma levels. Simultaneously, IFN beta-1b injection led to an immediate granulocytosis while concomitantly decreasing peripheral lymphocytes, especially natural killer (NK) cells. At the same time, IL-6, IL-10 and TNF-alpha plasma levels showed an overall increase. Overall, cytokine administration exerts strong stimulatory effects on the hypothalamic-pituitary-adrenal (HPA)-axis that may contribute to the side effects of IFN beta-1b therapy and affect the efficacy of IFN beta-1b treatment.

Longitudinal assessment of immuno-metabolic parameters in multiple sclerosis patients during treatment with glatiramer acetate.

Carrieri PB[1], Carbone F[2], Perna F[3], Bruzzese D[4], La Rocca C[2], Galgani M[2], Montella S[1], Petracca M[5], Florio C[6], Maniscalco GT[6], Spitaleri DL[7], Iuliano G[8], Tedeschi G[9], Corte MD[9], Bonavita S[9], Matarese G[10].

Author information

Abstract

OBJECTIVE: We investigated the effect of glatiramer acetate (GA) on the modulation of immune cell subpopulations and serum levels of **multiple** immune/**metabolic** markers in patients with relapsing-remitting **multiple sclerosis** (RRMS) to understand whether the treatment with GA could induce a specific change in the immunometabolic asset of patients with RRMS.

MATERIAL AND METHODS: We performed an extensive peripheral blood immunophenotyping and measured serum levels of several parameters involved in the pathogenesis of RRMS and also relevant in the pathogenesis of **metabolic syndrome** and obesity such as leptin, soluble leptin-receptor (sLep-R), myeloperoxidase (MPO), soluble CD40 ligand (sCD40-L), soluble tumor necrosis factor-receptor (sTNF-R), monocyte chemoattractant protein 1 (MCP-1), soluble Inter-Cellular Adhesion Molecule-1 (sICAM-1) and osteoprotegerin (OPG), in 20 naïve-to-treatment RRMS patients and 20 healthy controls. We repeated these analyses over time at 6 and 12months after starting GA treatment.

RESULTS: Our analysis showed that naïve-to-treatment RRMS patients had a lower number of $CD16^+CD56^+$ NK cells, $CD19^+$ B cells, $CD4^+$ T cells co-expressing the MHC class II activation marker HLA-DR ($CD4^+DR^+$) and naïve $CD4^+CD45RA^+$ T cells in basal conditions. GA treatment induced a specific and significant decrease of circulating $CD19^+$ B cells. Naïve-to-treatment RRMS patients also showed a significantly higher number of $CD4^+$ T cells with a memory phenotype ($CD4^+CD45RO^+$) whose peripheral frequency was not affected by GA treatment. These changes over time associated with a higher serum concentration of leptin and lower levels of MPO. GA treatment also reduced significantly the circulating levels of sCD40-L and sTNF-R overtime.

CONCLUSIONS: Our data suggest that the clinical outcome of GA treatment is associated with changes in immune cell subpopulations and modulation of specific immunometabolic markers. These data add substantial evidence of the immune modulating effect of GA during RRMS and could be of relevance in understanding the pathogenesis of disease and its follow-up.

Serum Adiponectin, TNF-α, IL-12p70, and IL-13 Levels in Multiple Sclerosis and the Effects of Different Therapy Regimens

Ugur Musabak[a] Seref Demirkaya[b] Gencer Genç[b] Rahsan Sagkan Ilikci[a]
Zeki Odabasi[b]

Departments of [a]Immunology and [b]Neurology, Gulhane Military Medical Academy and School of Medicine, Ankara, Turkey

Key Words
Multiple sclerosis · Pathogenesis · Adiponectin · Interleukin · Interferon · Glatiramer acetate

Abstract
Objectives: Multiple sclerosis (MS) is a chronic inflammatory disease of the human central nervous system. In the present study, we aimed to determine adiponectin, tumor necrosis factor-α, interleukin (IL)-12p70, and IL-13 levels in the sera of patients with MS and to investigate the effects of interferon (IFN), glatiramer acetate (GA), and immunosuppressive treatment regimens on these parameters. ***Methods:*** Fifty-seven patients with MS and 34 healthy controls were enrolled into the study. Serum cytokine levels were measured using enzyme immunoassay. ***Results:*** Significantly elevated levels of IL-12p70 and IL-13 were found in the sera of patients with MS, but decreased adiponectin levels were found in patients' sera compared to healthy controls. The levels of IL-12p70 and IL-13 in the IFN therapy group were higher than those of the healthy controls. However, the IL-12p70 and IL-13 levels in the GA therapy group were not different from those of the healthy controls. There were no differences with regard to adiponectin levels among the subgroups of patients with MS according to therapy regimen and the healthy controls. At the end of a 2-year follow-up period, Expanded Disability Status Scale (EDSS) values were found to be increased in the IFN therapy group but unchanged in the GA therapy group. ***Conclusions:*** These findings suggest that adiponectin, IL-12p70, and IL-13 may play a role in the pathogenesis of MS. Additionally, GA therapy regimens in MS are more effective than IFN therapy with respect to decreasing the levels of IL-12p70 and IL-13 and stabilizing the EDSS value.

Introduction

Multiple sclerosis (MS) is an autoimmune disease of the human central nervous system (CNS) that is characterized by inflammation, demyelination, and axonal injury. This disease often begins between the ages of 20 and 40 and affects woman more than men [1]. Although the etiology of MS is unknown, both genetic and environmental risk factors contribute to its development [2]. The immune system plays a central role in the pathogenesis of MS. It is well known that immune response against myelin antigens by autoreactive T lymphocytes is considered pivotal in MS pathogenesis [3]. Activated myelin-specific CD4+ T cells easily cross the blood-brain barrier and may recognize myelin antigens presented by astrocytes or microglia in brain parenchyma. Thereafter, they secrete proinflammatory cytokines and chemokines that may cause both the destruction of myelin sheaths of CNS neurons and the recruitment of other T cells and monocytes/macrophages [4]. In this context, cytokine studies have

Take home message

- I pazienti con SM presentano un basso rischio CV legato in parte alla disfunzione del SN simpatico
- I farmaci antipertensivi non modificano la storia e la prognosi della SM
- Dati promettenti con amiloride in termini di neuroprotezione
- Tra i DMT, natalizumab presenta il profilo CV migliore

È molto, molto difficile mettere d'accordo
cuore e cervello.
Pensa che, nel mio caso, non si
rivolgono nemmeno la parola.

Woody Allen