



XXXII Congreso Nacional de la SEMI

SEMI
LA VISIÓN GLOBAL DE LA PERSONA ENFERMA

FEMI
FEDERACIÓN CANARIA DE MEDICINA INTERNA



XIV Congreso de la Sociedad Canaria de Medicina Interna
26-28 Octubre 2011

Estatinas y Miopatía Una relación (controvertida) compleja

Albert Selva O'Callaghan
Barcelona, 27 de octubre de 2011

Costa Meloneras

Palacio de Congresos Expomeloneras
Maspalomas. San Bartolomé de Tirajana
Gran Canaria. Las Palmas

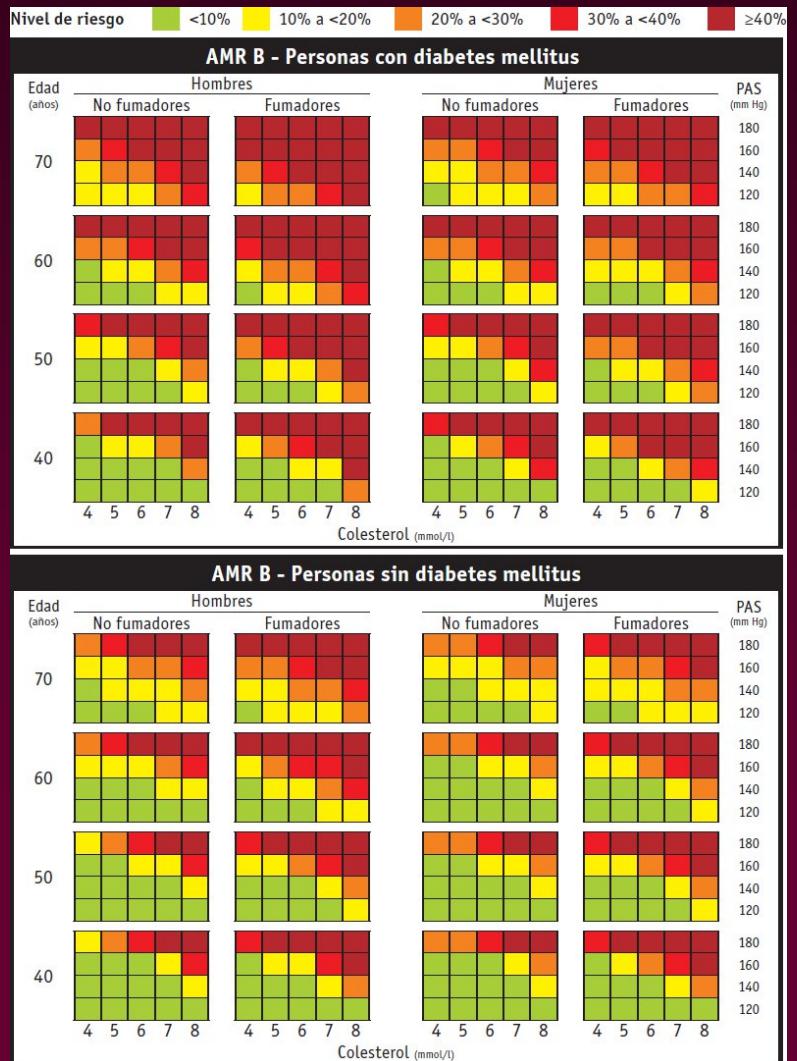
Magnitud del problema

↓ riesgo CV un 25%

Decenas de millones de sujetos en tratamiento

40% de sujetos deberían

1,5%-5% en ensayos clinicos !



Definición

Table 1. Proposed Definitions for Statin-Related Myopathy

Clinical Entity	ACC/AHA/NHLBI (2)	NLA (4)	FDA (3)
Myopathy	General term referring to any disease of muscles	Symptoms of myalgia (muscle pain or soreness), weakness, or cramps, plus creatine kinase $>10 \times$ ULN	Creatine kinase $\geq 10 \times$ ULN
Myalgia	Muscle ache or weakness without creatine kinase elevation	NA	NA
Myositis	Muscle symptoms with creatine kinase elevation	NA	NA
Rhabdomyolysis	Muscle symptoms with significant creatine kinase elevation (typically $>10 \times$ ULN), and creatinine elevation (usually with brown urine and urinary myoglobin)	Creatine kinase $>10\,000$ IU/L or creatine kinase $>10 \times$ ULN plus an elevation in serum creatinine or medical intervention with intravenous hydration	Creatine kinase $>50 \times$ ULN and evidence of organ damage, such as renal compromise

ACC/AHA/NHLBI = American College of Cardiology/American Heart Association/National Heart, Lung, and Blood Institute; FDA = U.S. Food and Drug Administration; NA = not available; NLA = National Lipid Association; ULN = upper limit of normal.

MIALGIAS
(1,5 veces más que los controles)

MIOSITIS

RABDOMIOLISIS

MIOPATÍA

(0,4 por 10.000 personas-año)

¿Fisiopatología?

Desestabilización
sarcolema (\downarrow colesterol)

Disfunción mitocondrial

Deplección isoprenoides

Coenzima Q10

Vitamina D

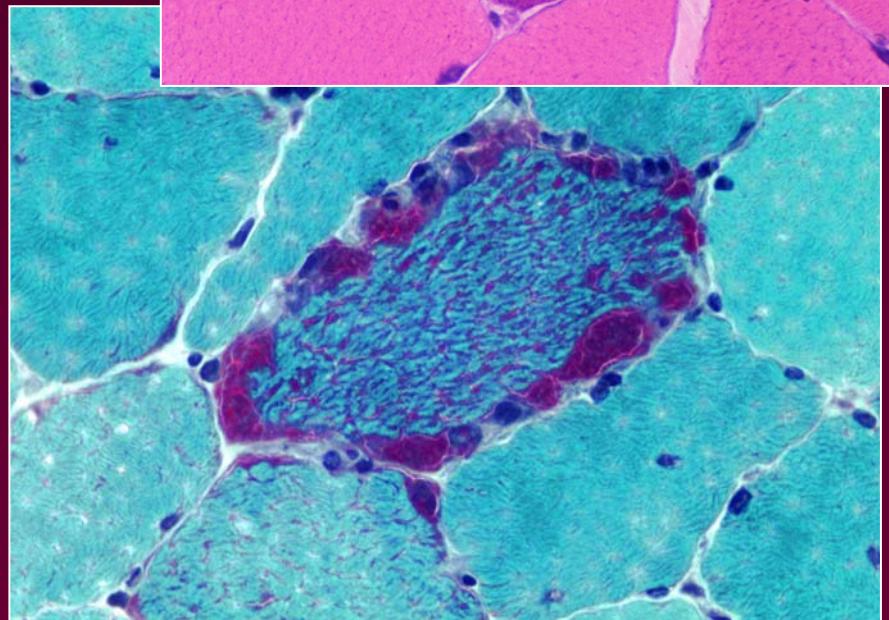
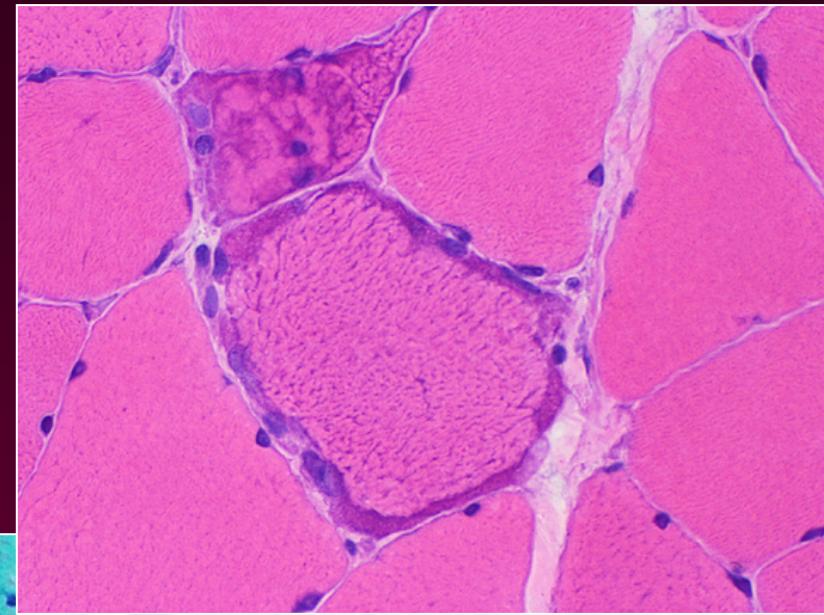
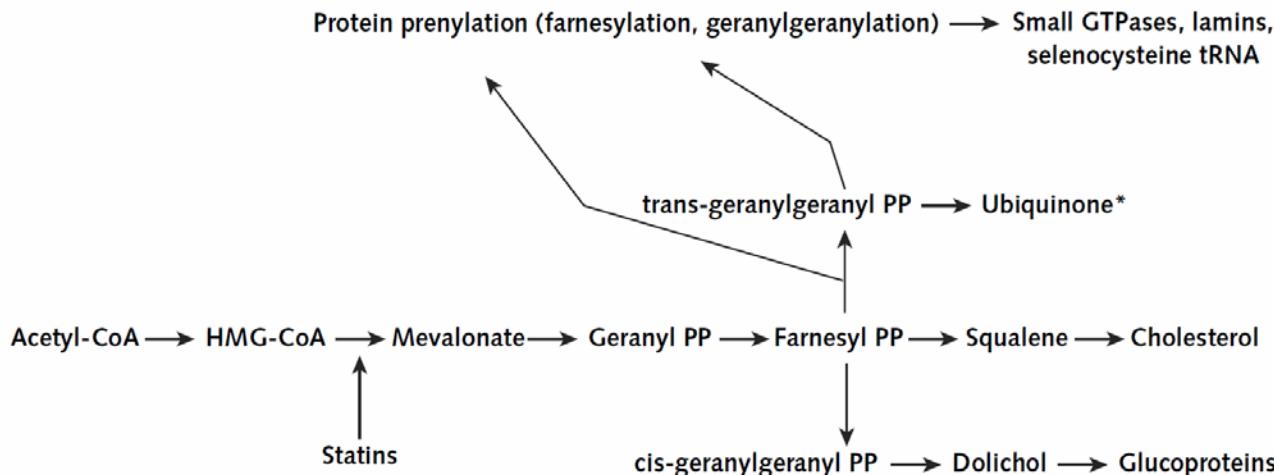
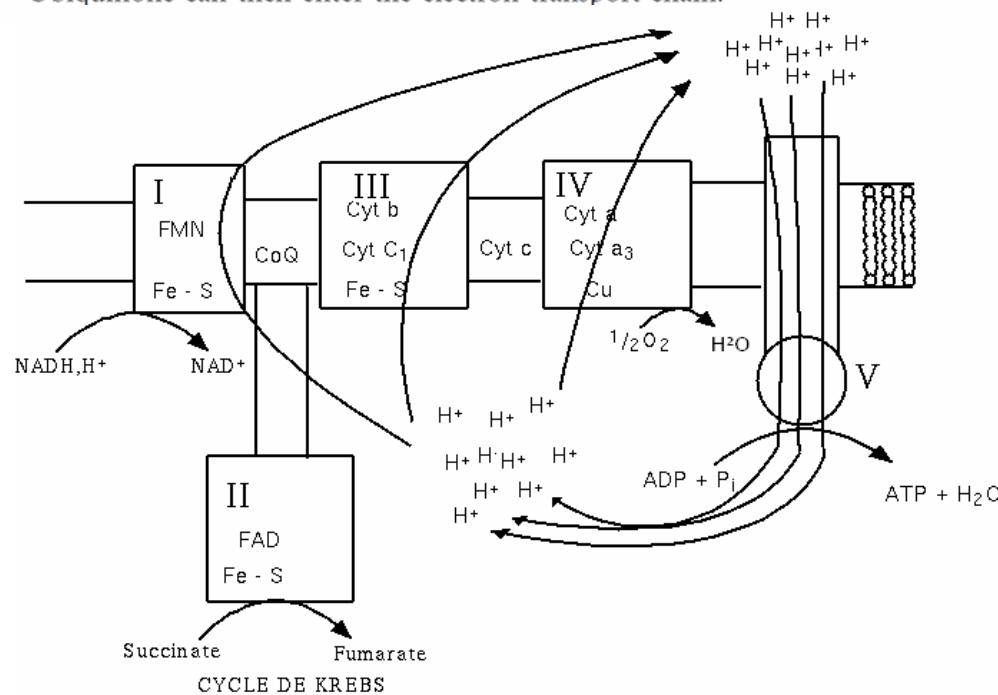


Figure. Synthesis of isoprenoids through the cholesterol biosynthetic pathway.



Acetyl-CoA = acetyl coenzyme A; GTP = guanine transfer protein; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; PP = pyrophosphate; tRNA = transfer ribonucleic acid.

* Ubiquinone can then enter the electron transport chain.



Importancia de la vitamina D

Original article

Vitamin D deficiency, myositis–myalgia, and reversible statin intolerance

Glueck CJ, et al

Current Medical Research & Opinion Vol. 27, No. 9, 2011, 1683–1690

150 pacientes 70 ♂, edad media 60 a,
intoleran > 1 estatina
< 32 ng/ml 25(OH)D

Suplementación 50.000 UI /s a los 8 meses (87% asintomáticos)
No suplementados (?)

¿Plausibilidad?

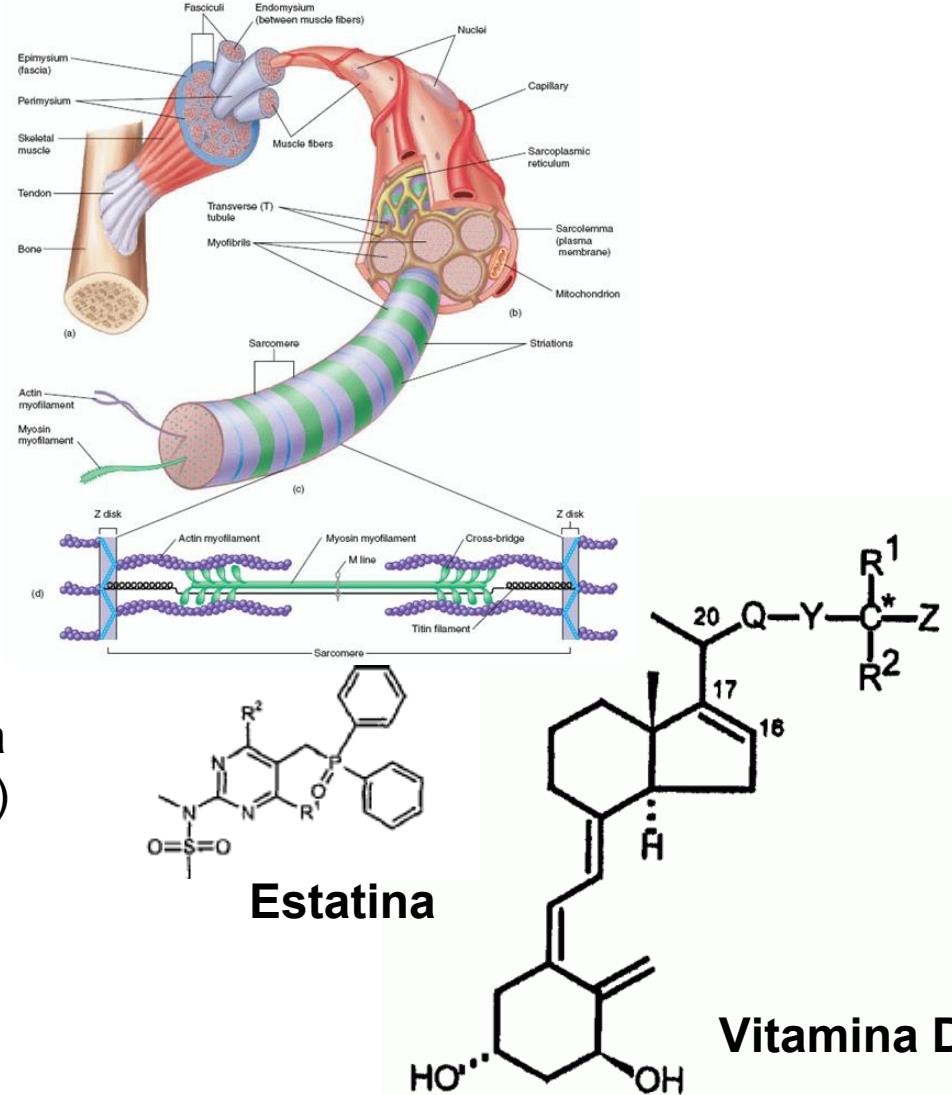
Miositis y valores bajos de vitamina D

Relación entre vitamina D y función física (ancianos)

Miocitos, R para vitamina D

CYP3A4 (si hidroxila vitamina D, reduciendo su disponibilidad para el metabolismo de las estatinas...)

A la espera de estudios aleatorizados



Factores de riesgo

Hipotiroidismo

OH

Zumo de pomelo

Miopatia familiar

Sexo femenino

Edad avanzada

Toxicidad muscular previa

CPK elevadas

Miopatia previa

Ciclosporina A

Macrólidos

Fibratos

Antifúngicos

Amiodarona

Verapamil

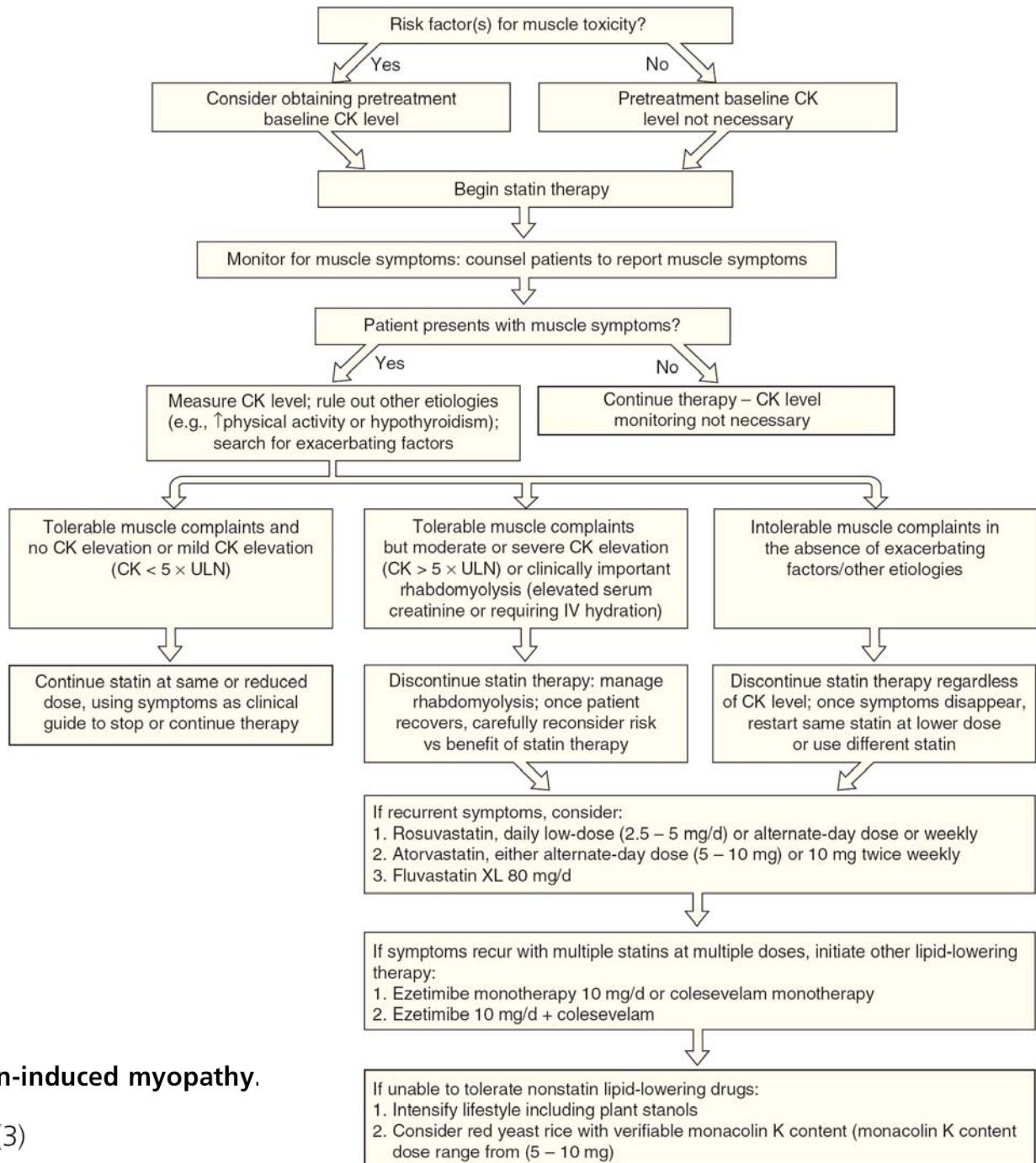
Fármacos antirretrovirales

Pravastatina
Fluvastatina
Rosuvastatina

[
-]

[
+]

Sinvastatina
Lovastatina
Atorvastatina



Caso clínico 1

(Varón 48 a)

Hipertensión, diabetes y
dislipemia

IQ cataratas en “árbol de Navidad”

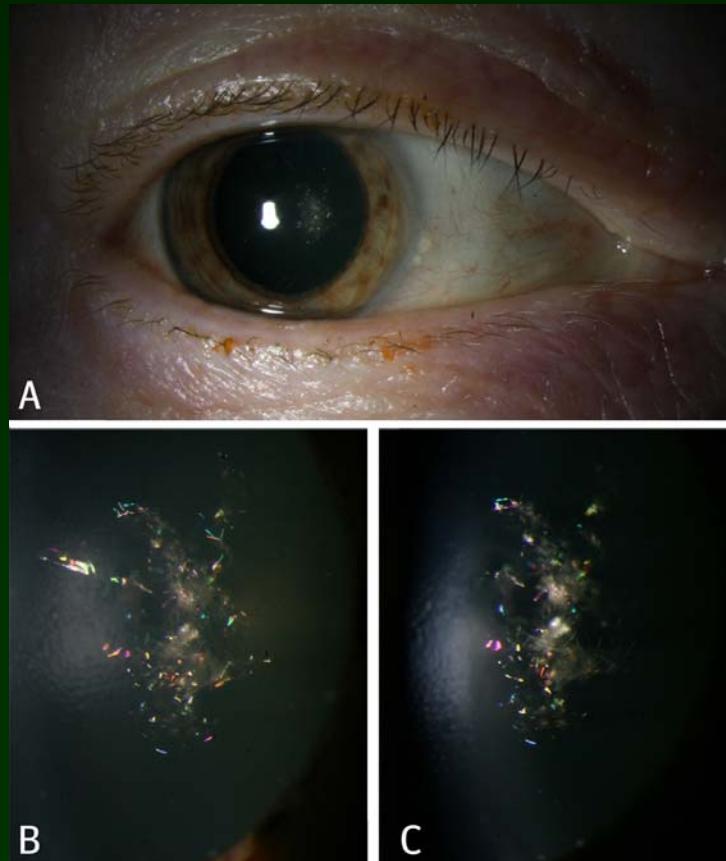
Pravastatina y a los 3 m

- Mialgias
- Fatiga
- Rigidez
- CPK > 1000 UI/l

EMG (descargas miotónicas)

Biopsia muscular

Estudio genético



Presymptomatic Neuromuscular Disorders Disclosed Following Statin Treatment

Georgios Tsivgoulis, MD; Konstantinos Spengos, MD; Nikolaos Karandreas, MD;
Marios Panas, MD; Athina Kladi, MS; Panagiota Manta, MD

Arch Intern Med. 2006;166:1519-1524

HIPOTIROIDISMO

MC ARDLE

MITOCONDRIAL (MELAS)

DISTROFIA MIOTÓNICA

ENFERMEDAD MN

MIOPATIA INFLAMATORIA (?)

Table. Baseline Characteristics, Medications, Symptoms, and Biochemical Investigations

Characteristic	Case No.			
	1	2	3	4
Age, y	48	62	51	58
Sex	Male	Male	Male	Male
History of NM disorders	Negative	Negative	Negative	Negative
Family history of NM symptoms	Negative	Negative	Negative	Negative
Statin	Pravastatin, 20 mg/d	Simvastatin, 20 mg/d	Atorvastatin, 40 mg/d	Pravastatin, 40 mg/d
Concomitant medications	Glibenclamide, 5 mg/d Perindopril, 4 mg/d	Glibenclamide, 5 mg/d Aspirin, 325 mg/d Metoprolol, 25 mg/d	Amiloride hydrochloride, 2.5 mg/d Hydrochlorothiazide, 25 mg/d	Allopurinol, 100 mg/d Aspirin, 100 mg/d Metoprolol, 50 mg/d Ramipril, 2.5 mg/d
Symptoms under statin treatment	Myalgias, muscle stiffness, fatigue	Fatigue	Rhabdomyolysis (myalgias, muscle stiffness, muscle cramps, diffuse muscle weakness, and dark urine)	Muscle twitching, muscle cramps, difficulty in climbing stairs
CK level				
Before statin treatment	Not measured	Normal*	Normal*	Not measured
During statin treatment	1125-1130 U/L	320-4400 U/L	45 100-48 300 U/L	850-1050 U/L
After ending statin treatment	578-730 U/L	825-1160 U/L	635-1030 U/L	435-565 U/L
Thyroid function†	Normal	Normal	Normal	Normal
Serum electrolytes‡	Normal	Normal	Normal	Normal

Miopatia inflamatoria y Estatinas

**Monitoring and Treatment of Dyslipidemia in IIM:
Results of the IMACS Survey**

**IMACS-ACR JDM Meeting
11-08-10**

**Christina Charles-Schoeman MD, MS
UCLA, USA**



Aim of Study

To Report the Experience/Clinical Practice of an Expert Panel of Health Care Providers and Researchers (IMACS) Regarding Monitoring and Treatment of Dyslipidemia

Methods: Dyslipidemia Questionnaire

- ⇒ Online survey of IMACs members
- ⇒ Questions regarding clinical practice

Frequency of lipid monitoring

Frequency of lipid lowering therapy use

Adverse effects with lipid lowering therapy

Results

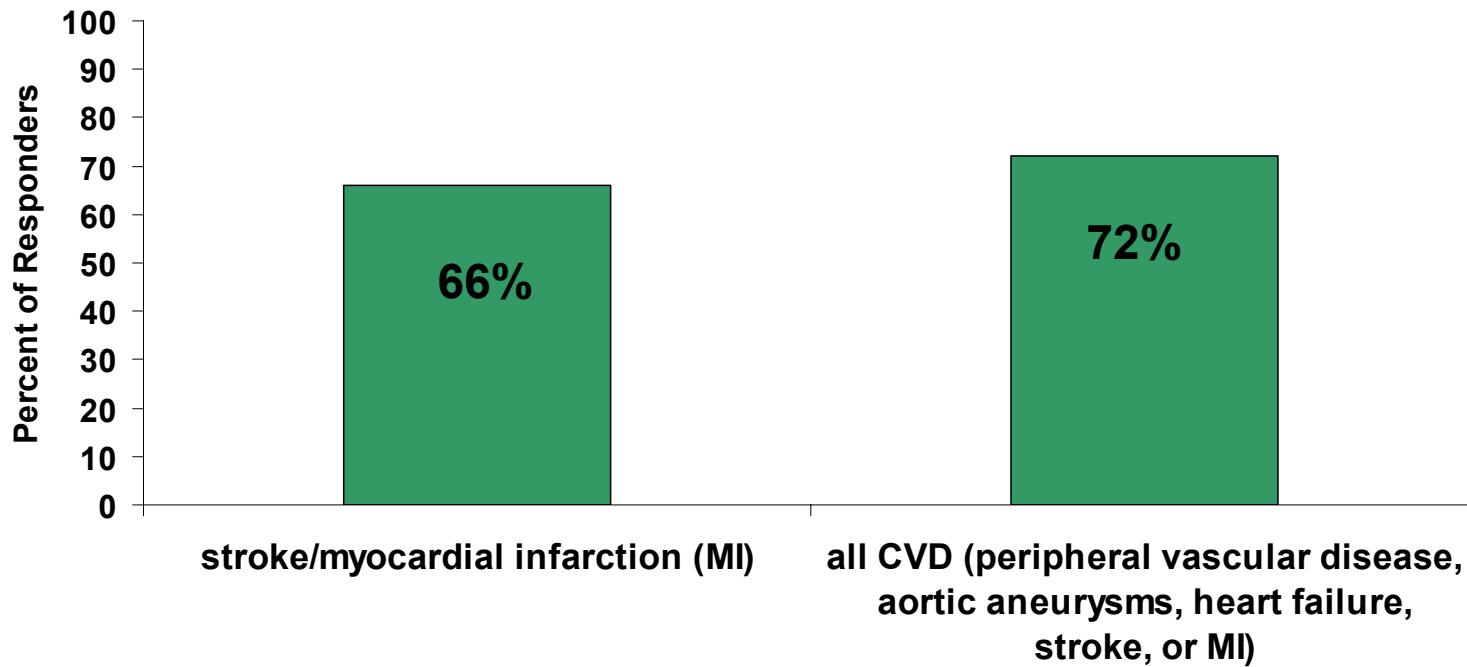
⇒ Participation: 63 IMACS Members
(37% response rate)

37% of responders treat > 50 IIM pts

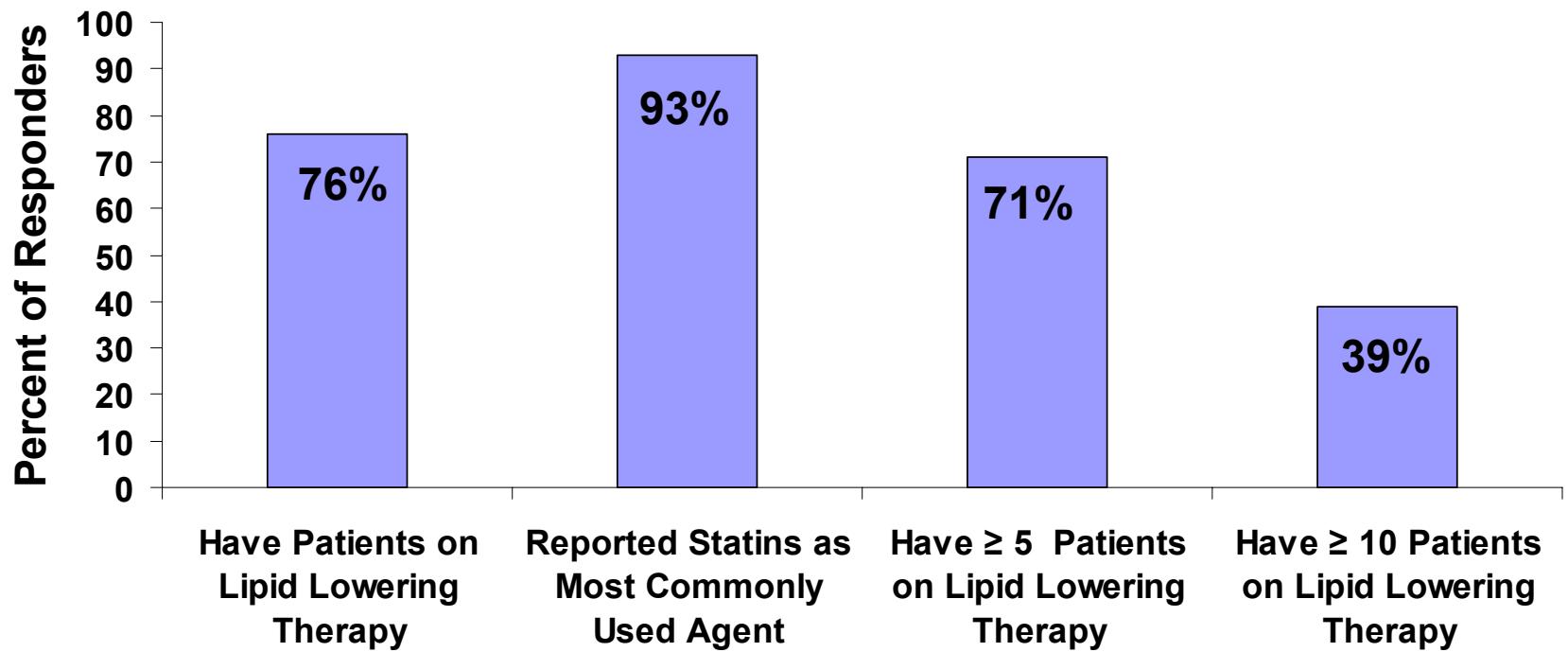
60% of responders treat > 20 IIM pts

(Minimum: 1641 IIM patients represented)

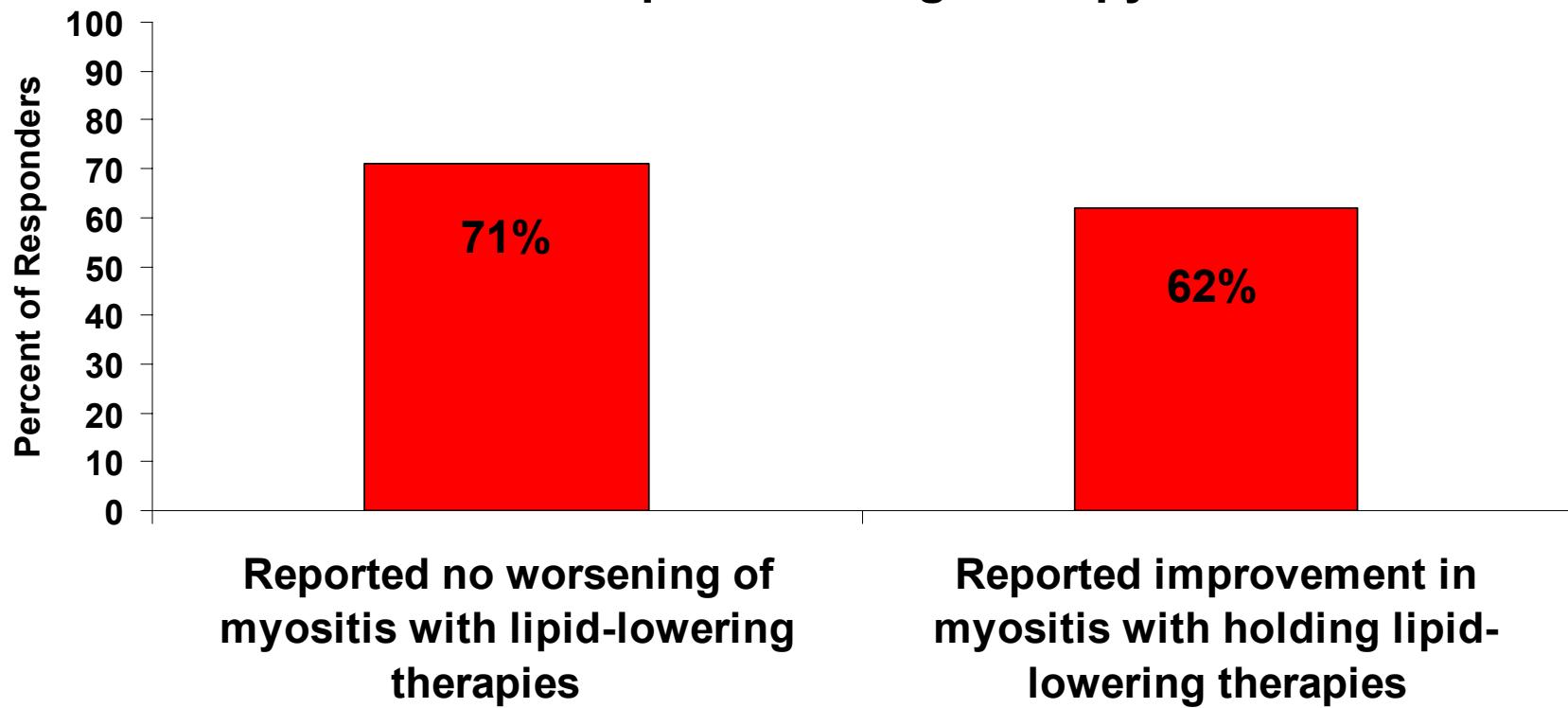
Treat Adult IIM Patients with Known CVD



Adult IIM—Responses Regarding Lipid Lowering Therapy



Side Effects of Lipid Lowering Therapy in Adult IIM



Conclusions

In a survey of specialists belonging to IMACS:

- ⇒ Statin Use in Adult Patients with Idiopathic Inflammatory Myopathies was Common.
- ⇒ The Majority of Specialists Reporting Statin Use Did Not Report Adverse Effects with Therapy.

Conclusions

- ⇒ Major Study Strength:
 - Expertise of Participants
- ⇒ Major Study Limitation:
 - Reliance on Participant Recall
- ⇒ Remaining Questions
 - Optimal therapy for dyslipidemia in IIM?
 - Safety of statins/other lipid-lowering therapies?
 - Relation of safety of lipid-lowering therapy to patient disease characteristics, disease activity?

Increased exposure to statins in patients developing chronic muscle diseases: a 2-year retrospective study

L Sailler,¹ C Pereira,¹ A Bagheri,¹ M Lapeyre-Mestre,¹ J L Montastruc,¹ P Arlet,² E Arlet-Suau,² E Uro-Coste,³ H Roussel,⁴ D Adoue,⁵ B Fournie,⁶ L Zabraniecki,⁶ M Laroche,⁷ P Cintas⁸

Ann Rheum Dis 2008;67:614–619.

“...la exposición a estatinas en pacientes > 50 años fue superior en aquellos diagnosticados de miopatía (21 DM/PM, 12 distrofias, 4 indeterminada, n=37) que en el grupo control (1 x 5)

“...la exposición a estatinas triplica el riesgo de desarrollar una miopatía inflamatoria a partir de los 50 años...”

IBM y estatinas

Aumento del colesterol en
cuerpos de inclusión

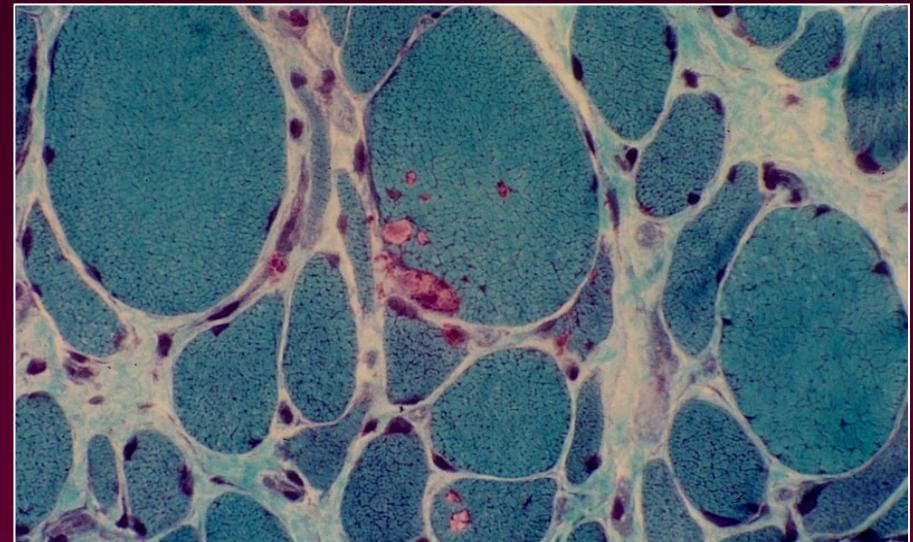
Efecto pleiotrópico

14 pacientes

- simvastatina 40 mg/d
- 12 meses

MMT 80, VAS, RNM, Biopsia,
gammagrafia deglutoria

Ninguno mejoró



Pilot trial of simvastatin in the treatment of sporadic inclusion body myositis
Sancricca C, et al. Neurol Sc 2011

Formas clínicas

Rabdomiólisis

Mialgias

Elevación asintomática de las CPK

Miopatia Necrotizante Inmuno Mediada (MNIM)

Caso clínico 2

(T.C.B. ♀ 57 a)

Natural de Paraguay

Debilidad proximal progresiva de
1 a de evolución

DMNID

Mialgias

Dislipemia hace 3 a en
tratamiento (atorvastatina 20
mg/d)

CPK 7.700

Retirada de Ca-VitD hace 4
meses

EMG actividad espontánea,
difuso

Estudio inmunológico y de
cribado de cáncer (-)

Evolución

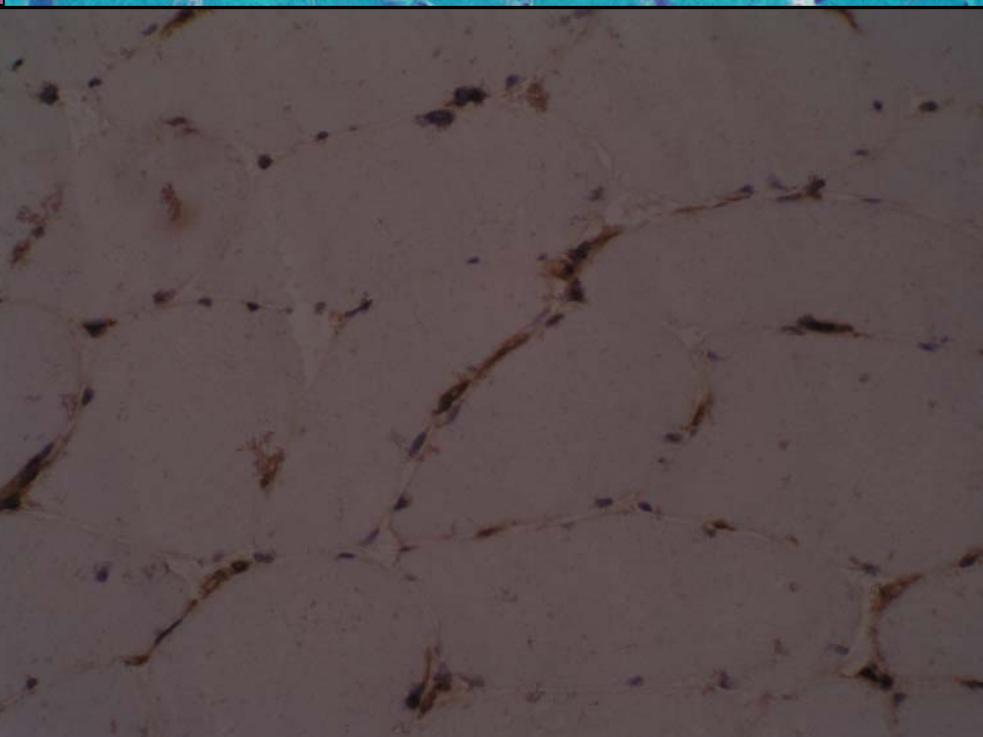
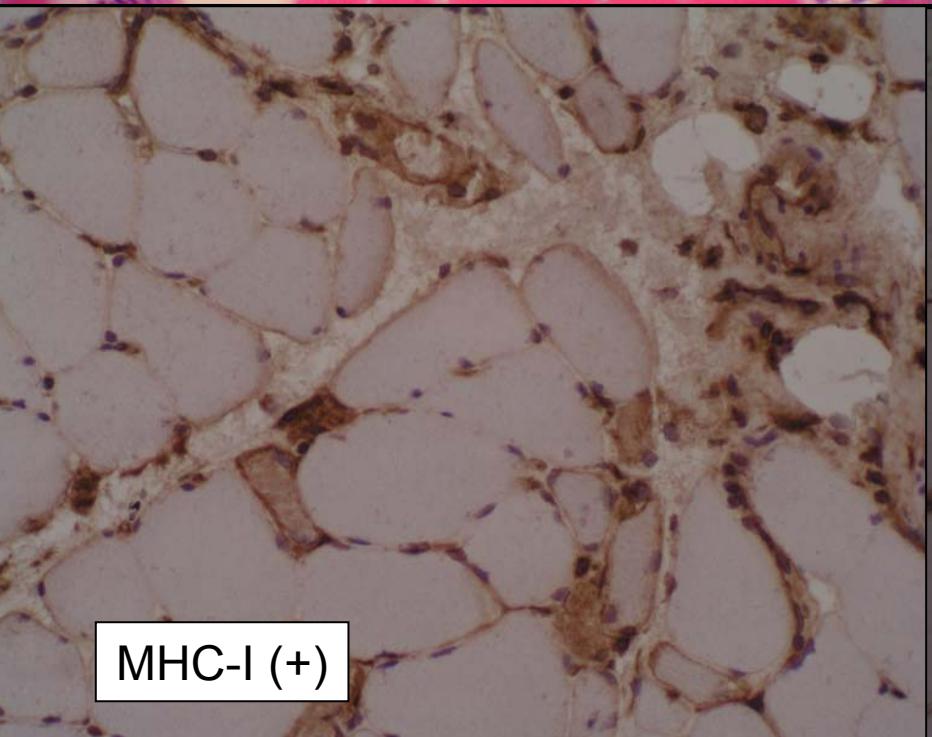
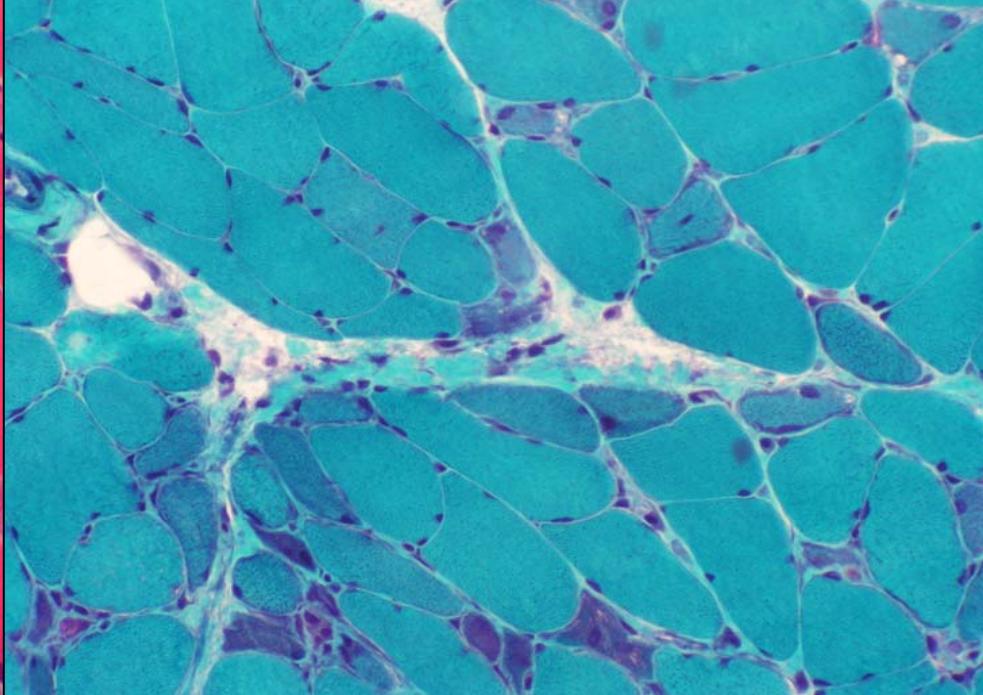
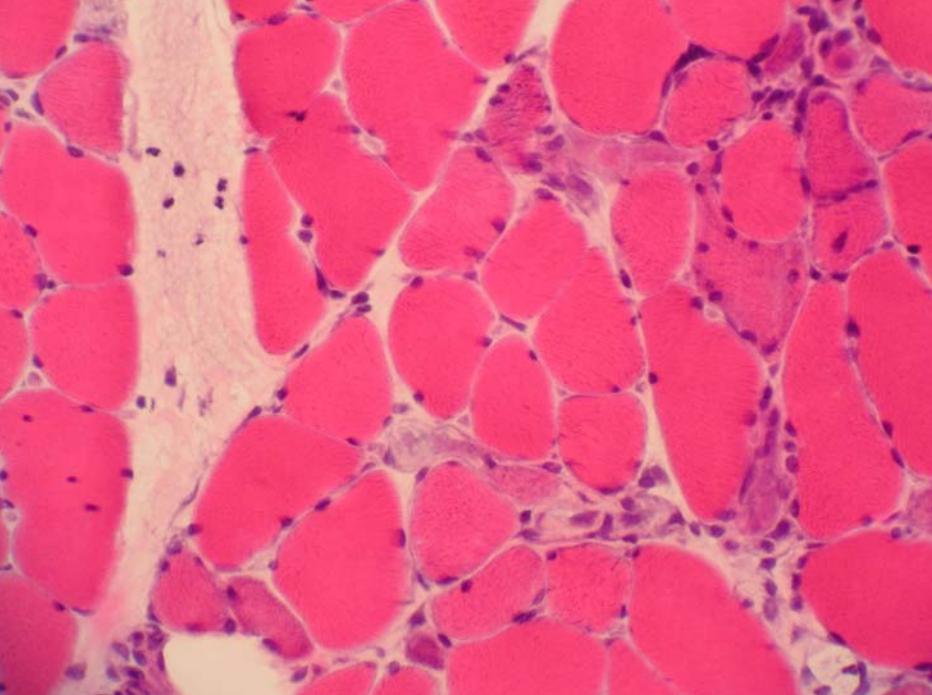
Biopsia muscular

- ➡ abundante necrosis de fibra muscular con escasa inflamación (macrófagos)
- ➡ expresión de MHC-I en células musculares (tb en las no necróticas)

Estudio IP

- ➡ no 100/200 kD (?)

- Tratamiento
 - retirada de estatinas
 - prednisona 1 mg/kg/d
 - azatioprina (TPMT) 75 mg/d
 - IGV (6 m) 0,4 gr/kg/d (x5)
- Hace 1 mes (CCEE), asintomática



MHC-I (+)

Miopatia Necrotizante Inmuno Mediada

Paraneoplásica

EXTENDED REPORT

Anti-signal recognition particle autoantibodies:
marker of a necrotising myopathy

G J D Hengstman, H J ter Laak, W T M Vree Egberts, I E Lundberg, H M Moutsopoulos,
J Vencovsky, A Doria, M Mosca, W J van Venrooij, B G M van Engelen

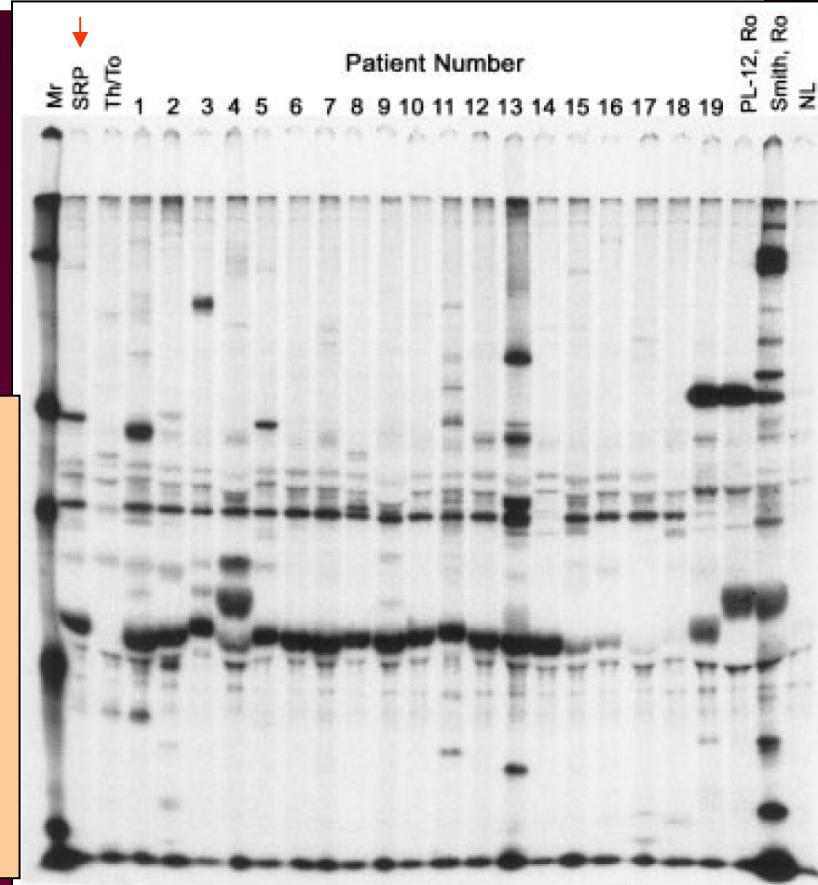


Ann Rheum Dis 2006;65:1635–1638. doi: 10.1136/ard.2006.052191

Asociada a anti-SRP

En relación a estatinas

Raza negra
Miocarditis
Curso fulminante
Miopatía
necrotizante





PERGAMON

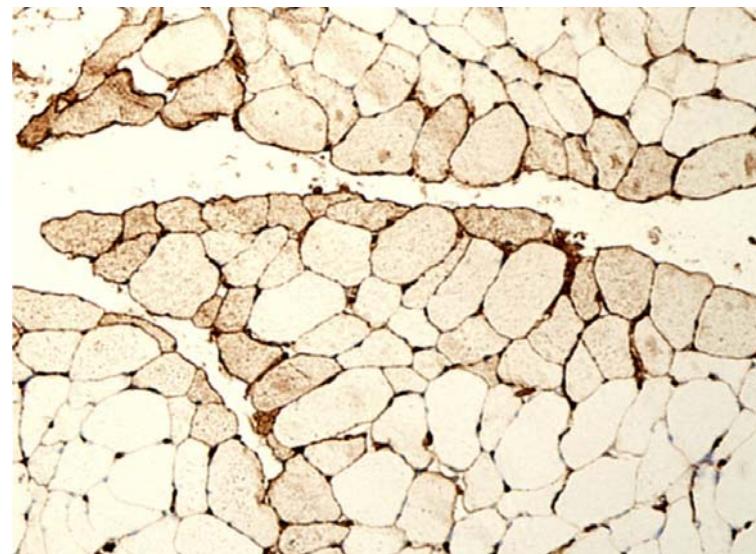
Neuromuscular Disorders 17 (2007) 194–200



www.elsevier.com/locate/nmd

Progressive myopathy with up-regulation of MHC-I associated with statin therapy

Merrilee Needham ^{a,*}, Victoria Fabian ^b, Wally Knezevic ^c, Peter Panegyres ^d,
Paul Zilko ^e, Frank L. Mastaglia ^a



IMMUNE-MEDIATED NECROTIZING MYOPATHY ASSOCIATED WITH STATINS

PHYLLIS GRABLE-ESPOSITO, MD,¹ HANS D. KATZBERG, MD,² STEVEN A. GREENBERG, MD,¹

JAYASHRI SRINIVASAN, MD, PhD,^{3,4} JONATHAN KATZ, MD,⁵ and ANTHONY A. AMATO, MD¹

¹ Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

² Department of Neurology, Stanford University Medical Center, Stanford, California, USA

³ Department of Neurology, Lahey Clinic, Burlington, Massachusetts, USA

⁴ Department of Neurology, Tufts Medical School, Boston, Massachusetts, USA

⁵ Department of Neurology, California Pacific Medical Center, San Francisco, California, USA

Muscle Nerve 41: 185–190, 2010

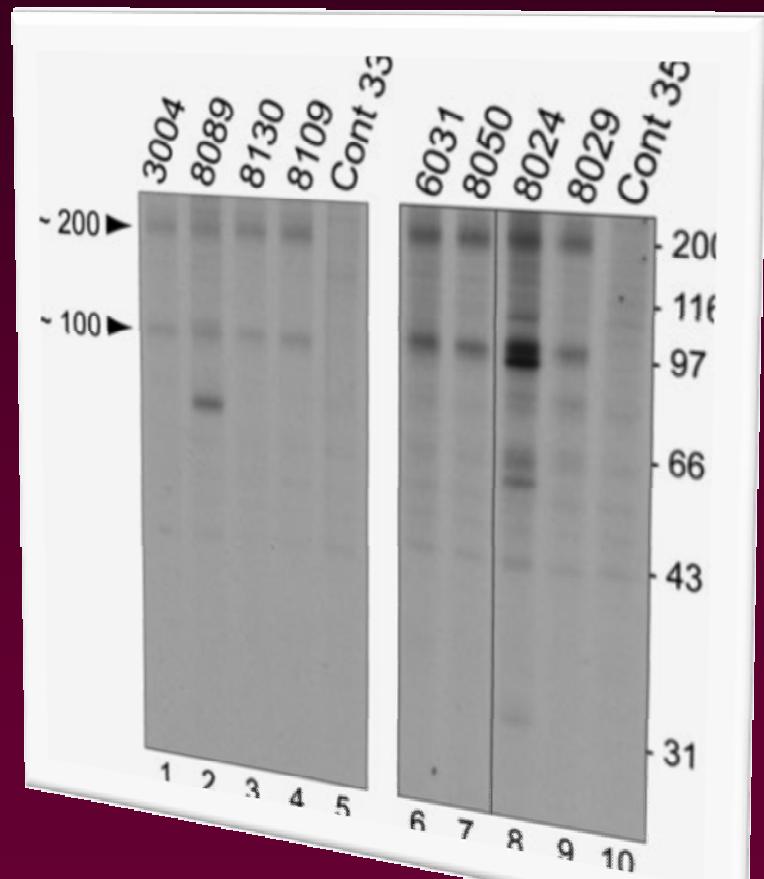
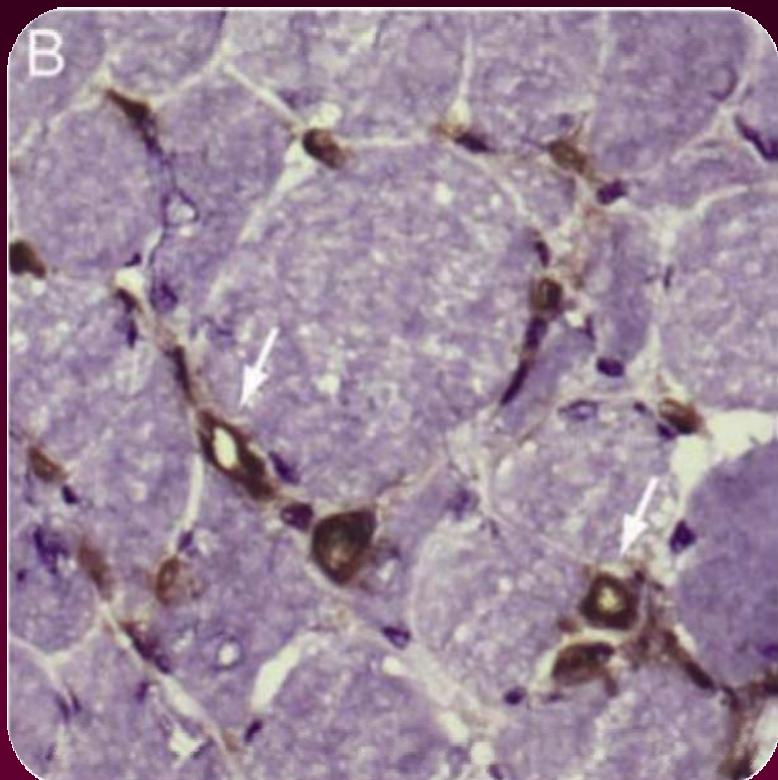
Table 2. Comparison of necrotizing myopathy to other inflammatory myopathy cases in terms of statin exposure and age.

	Number of patients	Number of patients exposed to statin	Percent of patients exposed to statin	P-value for statin exposure	Mean age (years)	P-value for age vs. NM group
NM	22	18	82%		65.5	
IBM	50	19	38%	0.0006	60.6	0.09
PM	33	8	24%	<0.0001	52.6	0.0005
DM	33	6	18%	<0.0001	45.4	7.36×10^{-7}

1. Debilidad muscular proximal durante o tras tratamiento con estatinas
2. CPK elevadas
3. Persistencia de 1 y 2 tras la retirada de estatinas
4. Mejoría con tratamiento ID
5. Miopatia Necrotizante IM

Miopatía Necrotizante Inmunomediada

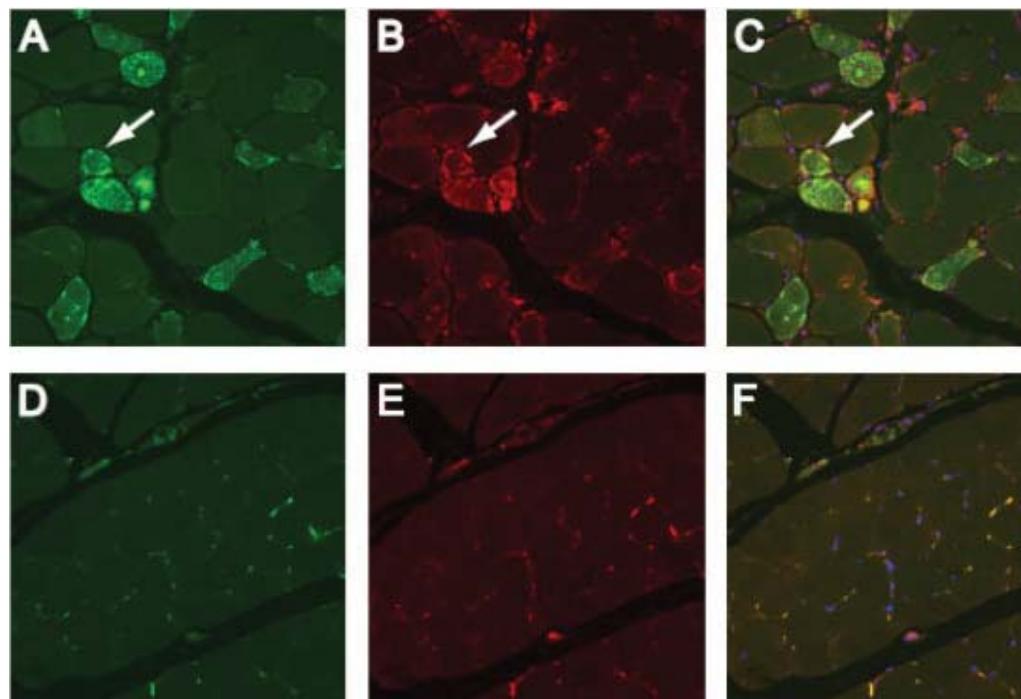
Anti-200/100 kD



A novel autoantibody recognizing 200-kd and 100-kd proteins
is associated with an immune-mediated necrotizing myopathy
Christopher-Stine L, et al. Arthritis & Rheum 2010

Autoantibodies Against 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase in Patients With Statin-Associated Autoimmune Myopathy

Andrew L. Mammen, Tae Chung, Lisa Christopher-Stine, Paul Rosen,
Antony Rosen, Kimberly R. Doering, and Livia A. Casciola-Rosen



Preguntas frecuentes

¿En pacientes con valores elevados de CPK se pueden administrar estatinas?

< de 2.500 UI/l (x 10) en pacientes asintomáticos

¿Se pueden volver a reintroducir, y cuando?

Rosuvastatina

a dosis bajas (5 mg) y a días alternos (75%)
el objetivo terapéutico se alcanzó (65%)

¿Cuándo hay que retirarlas?

¿Cuál es la estrategia?

Estrategia

Miotoxicidad dosis dependiente

Detectar pacientes de riesgo

⇒ polimorfismo

[SNP, s4363657,
gen *SLCO1B1*,
cromosoma 12]

(*N Engl J Med* 2008)

Importancia de las interacciones (P 450)

Asociación entre ezetimiba y estatinas

⇒ anti-HMG (100/200 kD)

Coenzima Q10 (100 mg/d)

Anti-HMG-CoA reductase antibodies are rare in statin users, including those with self-limited musculoskeletal side-effects

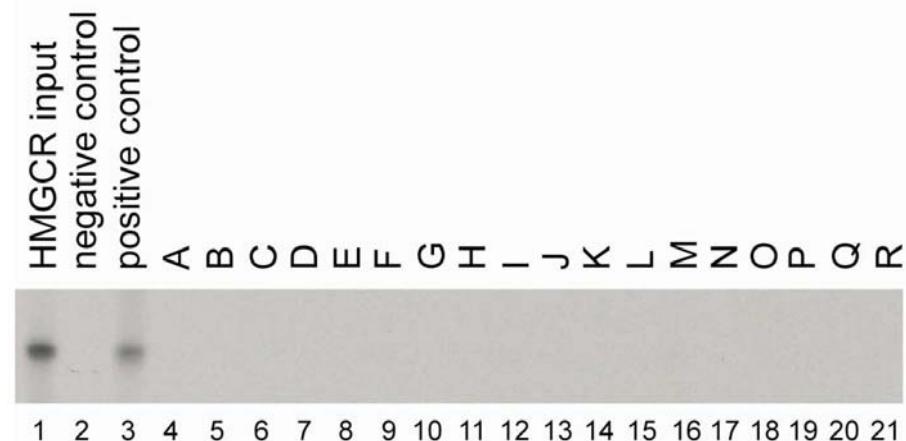
Andrew L. Mammen, MD, PhD, Katherine Pak, MD, Emma K. Williams, MHS, Diane Brisson, PhD, CCRP, Joe Coresh, MD, PhD, Elizabeth Selvin, PhD, MPH*, Daniel Gaudet, MD, PhD*

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Significance and Innovation

1. Anti-HMGCR antibodies are not found in the vast majority of statin-treated subjects, including those with self-limited statin-associated myopathy.
2. The presence of anti-HMGCR antibodies is highly specific for subjects with an autoimmune myopathy requiring immunosuppression.

Figure 1



Mensajes

La presencia de miopatía o valores elevados de CK no contraindica la administración de estatinas

Valorar relación riesgo / beneficio

Las estatinas pueden desenmascarar una miopatía no diagnosticada

La disminución de dosis, cambio de estatina o administración de vitamina D (?) forman parte de la estrategia terapéutica

Área de intensa investigación (polimorfismos, anti-HMG, relación con miopatia inflamatoria...)