Tratamientos de la amiloidosis TTR

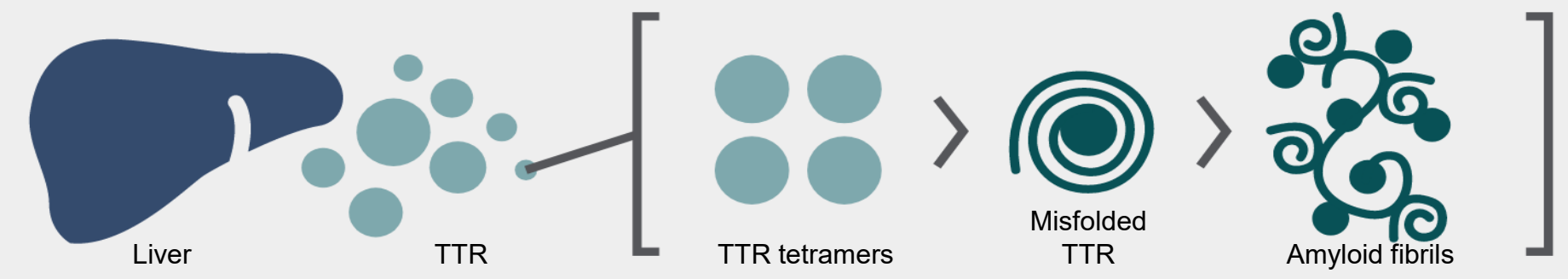
Carlos Casasnovas
Unidad de Neuromusuclar
Unidad Multidisciplinar de Amiloidosis Familiar
Hospital Universitari de Bellvitge - IDIBELL

UNIVERSITAT DE BARCELONA

IDIBELL
Institut d'Investigació Biomèdica de Bellvitge

Bellvitge
Hospital Universitari

Estrategias Terapéuticas



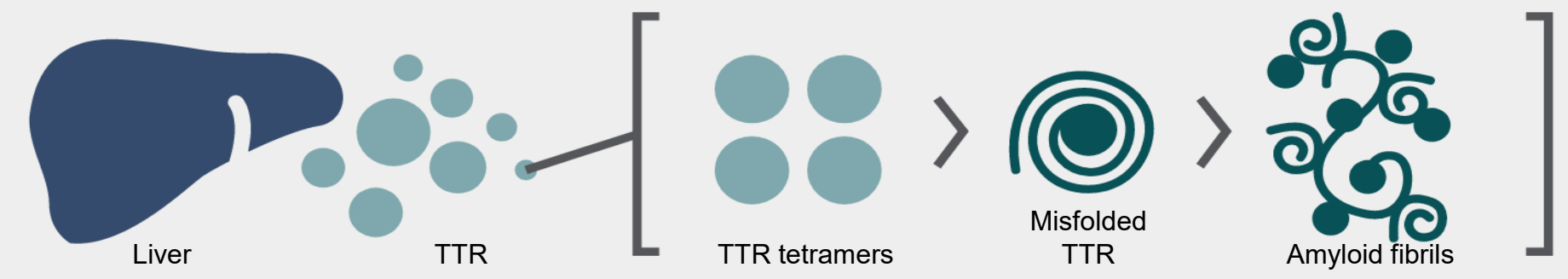
Suppression of TTR synthesis
- ONPATTRO™ (patisiran)[1,a,b]
- TEGSEDI™ (inotersen)[2,b]
- Orthotopic liver transplantation (OLT)[3]

TTR stabilization
- Tafamidis[4]
- Diflunisal[5,6]
- SOM0226

Fibril degradation and reabsorption (investigational)
- Doxycycline + TUDCA[7]
- Anti-SAP antibody[8]

[a]Approved in the US; [b]Approved in the EU
SAP, serum amyloid P; TUDCA, tauroursodeoxycholic acid
1. Adams et al. N Engl J Med 2018;379:11-21; 2. Benson et al. N Engl J Med 2018; 379:22-31; 3. Ando et al. Orphanet J Rare Dis 2013;8:3; 4. Said et al. Nat Rev Drug Dis 2012;11:185–186; 5. Berk et al. JAMA 2013;310:2658–2667; 6. National Amyloidosis Centre. ATTR Amyloidosis. 2014. Available from: http://www.amyloidosis.org.uk/introduction-to-attr-amyloidosis/. [Accessed October 2016]; 7. Obici et al. Amyloid 2012;19(Suppl 1):34–6; 8. Richards et al. N Engl J Med 2015;373:1106–1114

Estrategias Terapéuticas



Suppression of TTR synthesis
- ONPATTRO™ (patisiran)[1,a,b]
- TEGSEDI™ (inotersen)[2,b]
- Orthotopic liver transplantation (OLT)[3]

TTR stabilization
- Tafamidis[4]
- Diflunisal[5,6]
- SOM0226

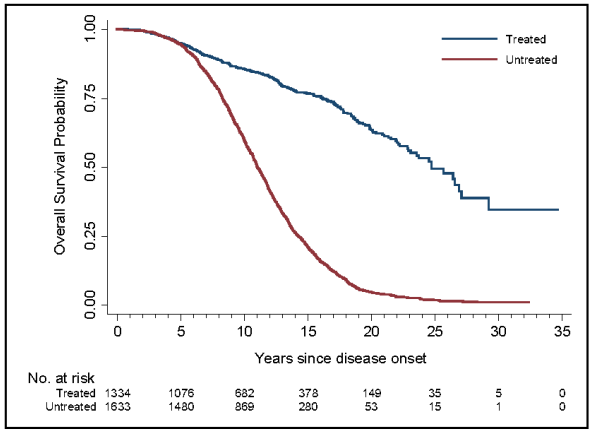
Fibril degradation and reabsorption (investigational)
- Doxycycline + TUDCA[7]
- Anti-SAP antibody[8]

[a]Approved in the US; [b]Approved in the EU
SAP, serum amyloid P; TUDCA, tauroursodeoxycholic acid
1. Adams et al. N Engl J Med 2018;379:11-21; 2. Benson et al. N Engl J Med 2018; 379:22-31; 3. Ando et al. Orphanet J Rare Dis 2013;8:3; 4. Said et al. Nat Rev Drug Dis 2012;11:185–186; 5. Berk et al. JAMA 2013;310:2658–2667; 6. National Amyloidosis Centre. ATTR Amyloidosis. 2014. Available from: http://www.ucl.ac.uk/amyloidosis/clinical-info/introduction-to-attr-amyloidosis. [Accessed October 2016]; 7. Obici et al. Amyloid 2012;19(Suppl 1):34–6; 8. Richards et al. N Engl J Med 2015;373:1106–1114

Tranplante Hepático

- 1991 primer trasplante hepático
- No efecto significativo en complicaciones de SNC ni oculares
- Puede haber progresión síntomas cardíacos (29%), SNC y oculares
- Algunos progresan

TTR-FAP overall treatment can be associated to a 76% reduction in mortality risk compared with natural history: 11 years *vs* 25 years median TTR-FAP survival

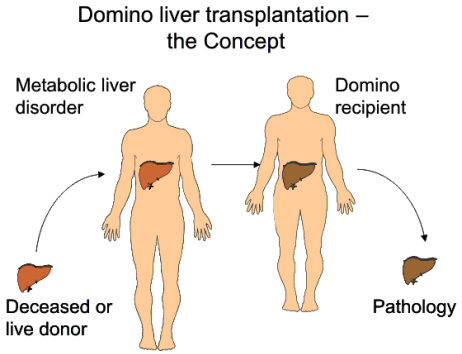


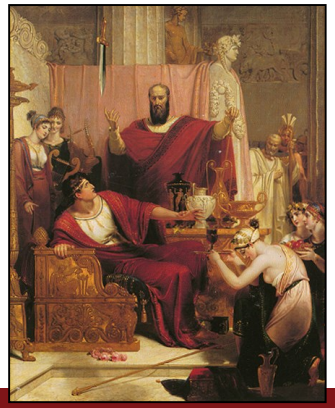
	mOS (years)	95% CI
All Treated	24.73	23.09-27.09
All Untreated	11.05	10.80-11.38

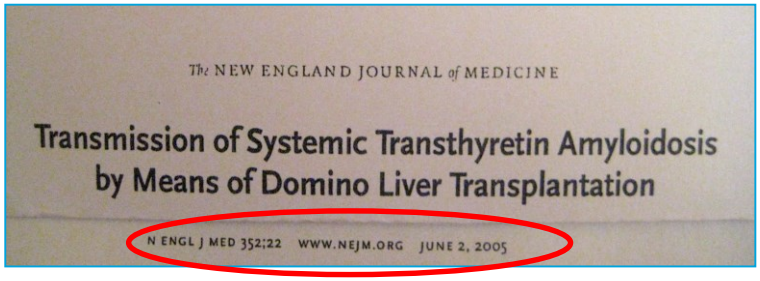
Holmgren G 1991
Herlenius G, 2004;
Okamoto S, 2009;
Hara R, 2010
Ohya Y, 2011

Tranplante Hepático en dominó

- En areas como Portugal con una prevalencia elevada: Aumento de la lista de espera
- 1993 First International Workshop in Liver Transplantation for FAP
- 1995 Portugal primer transplante en dominó (THD)

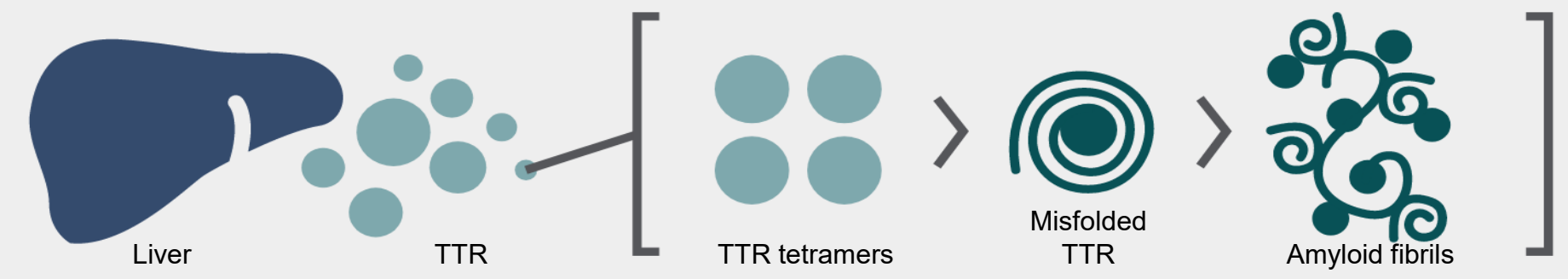






Takei Y, 2007
Stangou AJ, 2005

Estrategias Terapéuticas



Suppression of TTR synthesis
- ONPATTRO™ (patisiran)[1,a,b]
- TEGSEDI™ (inotersen)[2,b]
- Orthotopic liver transplantation (OLT)[3]

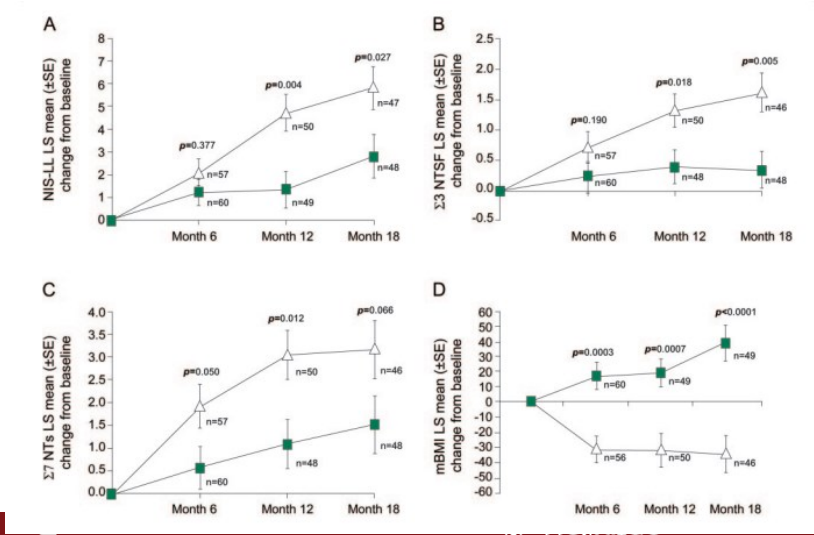
TTR stabilization
- Tafamidis[4]
- Diflunisal[5,6]
- SOM0226

Fibril degradation and reabsorption (investigational)
- Doxycycline + TUDCA[7]
- Anti-SAP antibody[8]

[a]Approved in the US; [b]Approved in the EU
SAP, serum amyloid P; TUDCA, tauroursodeoxycholic acid
1. Adams et al. N Engl J Med 2018; 379:22-31; 2. Benson et al. N Engl J Med 2018; 379:22-31; 3. Ando et al. Orphanet J Rare Dis 2013;8:3; 4.

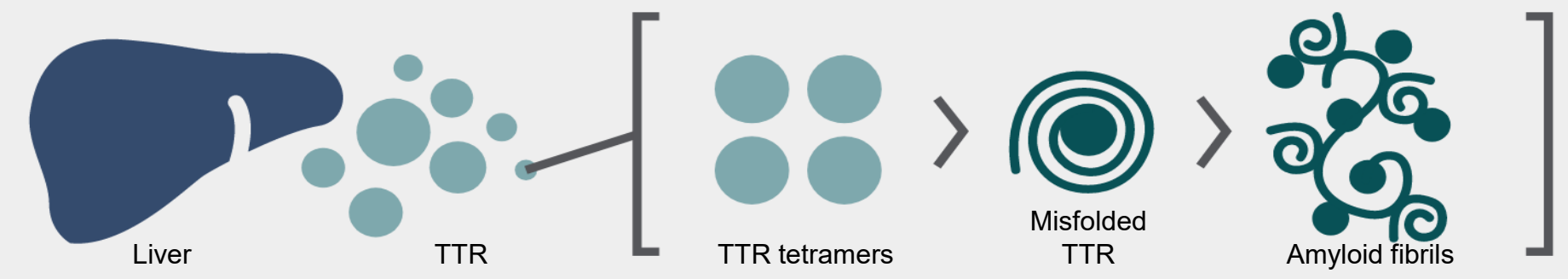
Tafamidis

- 60% de no progresión en 1 año en FAP vs 38% de placebo
- IMC se deterioro en placebo y no en Tafamidis
- 52% menos deterioro neurológico en Tafamidis
- Minima progresión de la enfermedad a los 5,5 años de evolución
- European Medical Agency for patients in stage I of neuropathic ATTR.



Coelho T, 2012
Berk JL, 2011
Suhr OB 2016
Gillmore JD, 2017

Estrategias Terapéuticas



Suppression of TTR synthesis
- ONPATTRO™ (patisiran)[1,a,b]
- TEGSEDI™ (inotersen)[2,b]
- Orthotopic liver transplantation (OLT)[3]

TTR stabilization
- Tafamidis[4]
- Diflunisal[5,6]
- SOM0226

Fibril degradation and reabsorption (investigational)
- Doxycycline + TUDCA[7]
- Anti-SAP antibody[8]

[a]Approved in the US; [b]Approved in the EU

SAP, serum amyloid P; TUDCA, tauroursodeoxycholic acid

1. Adams et al. N Engl J Med 2018;379:11-21; 2. Benson et al. N Engl J Med 2018; 379:22-31; 3. Ando et al. Orphanet J Rare Dis 2013;8:3; 4. Said et al. Nat Rev Drug Dis 2012;11:185–186; 5. Berk et al. JAMA 2013;310:2658–2667; 6. National Amyloidosis Centre. ATTR Amyloidosis. 2014. Available from: http://www.amyloidosis.org.uk/ introduction-to-attr-amyloidosis/ [Accessed October 2016]; 7. Obici et al. Amyloid 2012;19(Suppl 1):34–6; 8. Richards et al. N Engl J Med 2015;373:1106–1114

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 5, 2018 VOL. 379 NO. 1

Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis

D. Adams, A. Gonzalez-Duarte, W.D. O'Riordan, C.-C. Yang, M. Ueda, A.V. Kristen, I. Tournev, H.H. Schmidt, T. Coelho, J.L. Berk, K.-P. Lin, G. Vita, S. Attarian, V. Planté-Bordeneuve, M.M. Mezei, J.M. Campistol, J. Buades, T.H. Brannagan III, B.J. Kim, J. Oh, Y. Parman, Y. Sekijima, P.N. Hawkins, S.D. Solomon, M. Polydefkis, P.J. Dyck, P.J. Gandhi, S. Goyal, J. Chen, A.L. Strahs, S.V. Nochur, M.T. Sweetser, P.P. Garg, A.K. Vaishnaw, J.A. Gollob, and O.B. Suhr

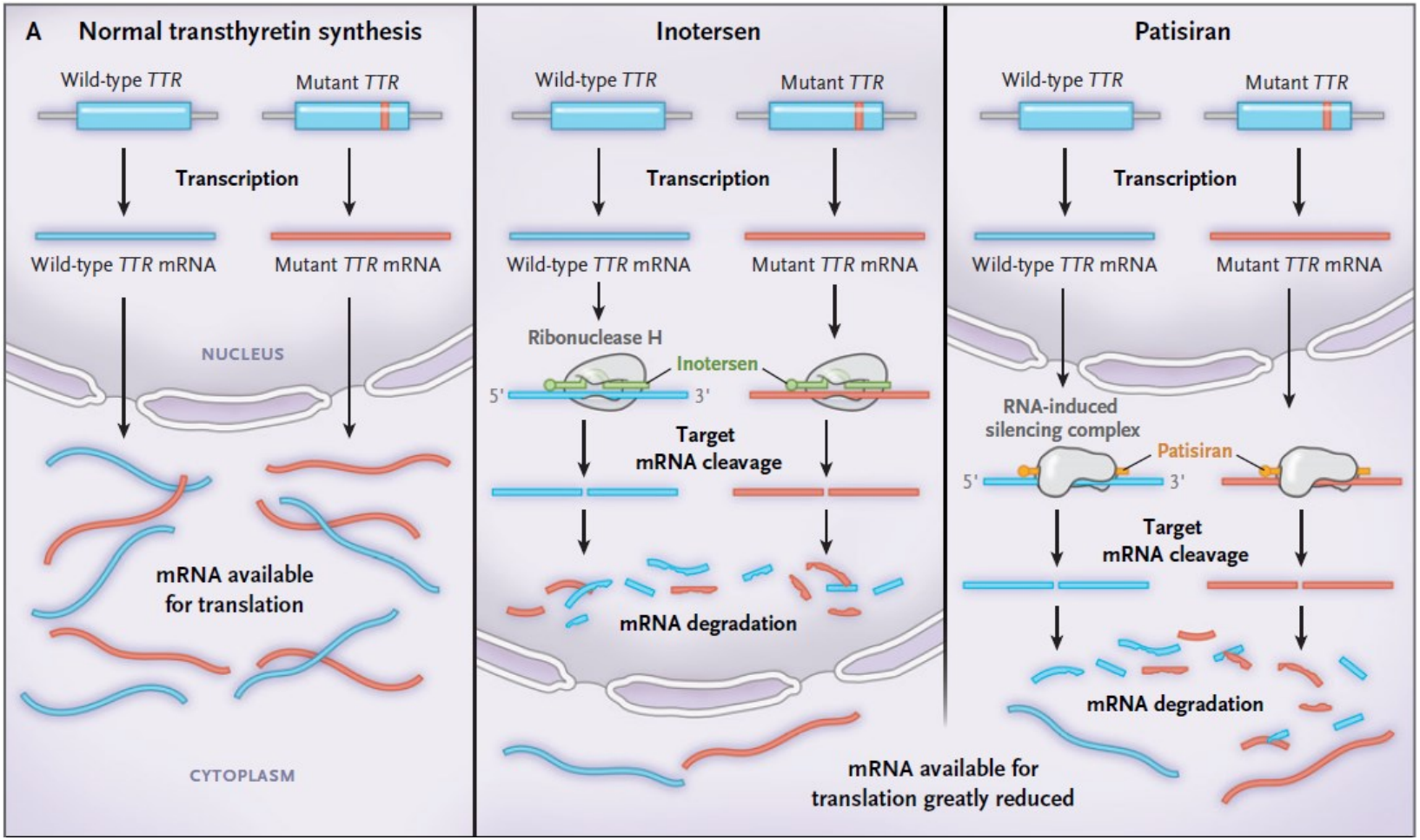
ORIGINAL ARTICLE

Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis

M.D. Benson, M. Waddington-Cruz, J.L. Berk, M. Polydefkis, P.J. Dyck, A.K. Wang, V. Planté-Bordeneuve, F.A. Barroso, G. Merlini, L. Obici, M. Scheinberg, T.H. Brannagan III, W.J. Litchy, C. Whelan, B.M. Drachman, D. Adams, S.B. Heitner, I. Conceição, H.H. Schmidt, G. Vita, J.M. Campistol, J. Gamez, P.D. Gorevic, E. Gane, A.M. Shah, S.D. Solomon, B.P. Monia, S.G. Hughes, T.J. Kwoh, B.W. McEvoy, S.W. Jung, B.F. Baker, E.J. Ackermann, M.A. Gertz, and T. Coelho

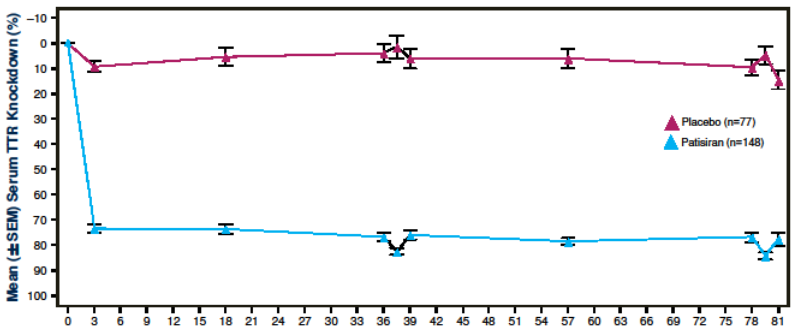
Note comparisons cannot be made between studies.
Inotersen is indicated for the treatment of stage 1 or stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR).

Antisense and RNA Interference
Comparison of Mechanism of Action

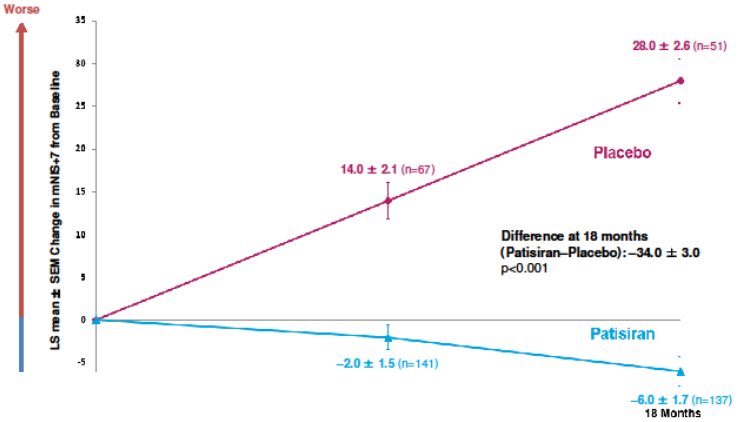


Estudio Apollo. Resultados

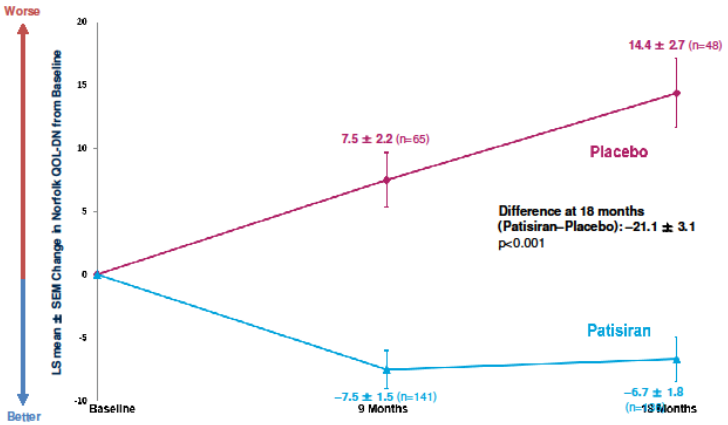
Reducción de TTR en suero



mNIS+7: Cambio desde la linea de base



Norfolk QOL-DN: Cambio desde la linea de base



Adams et al. *N Engl J Med* 2018;378:11-21.

Estudio Apollo. Resultados

Seguridad y Tolerabilidad. Efectos adversos

Majority of AEs were mild or moderate in severity

- Peripheral edema
  - Did not result in any treatment discontinuations
  - Decreased over time
- Infusion-related reactions (IRRs)
  - Majority mild in severity
  - No severe, life-threatening or serious IRRs
  - Decreased over time
  - Led to treatment discontinuation in 1 patient

No safety signals regarding cataracts, hyperglycemia, infection, or osteopenia/ osteoporosis

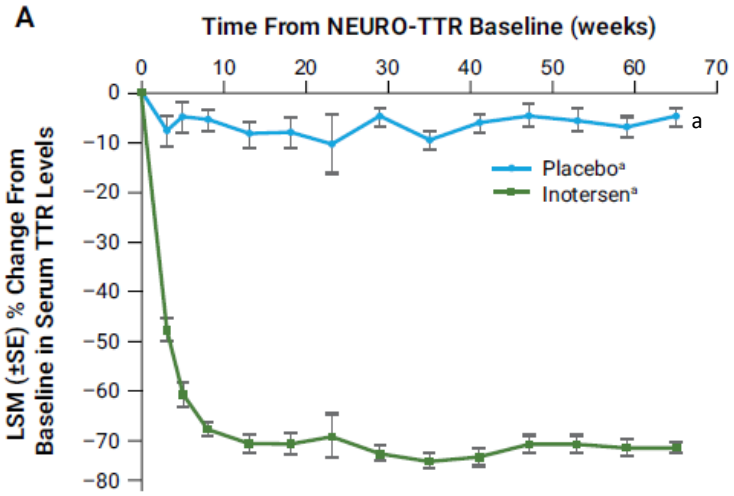
No safety signals regarding liver function tests, hematology including thrombocytopenia, or renal dysfunction related to patisiran

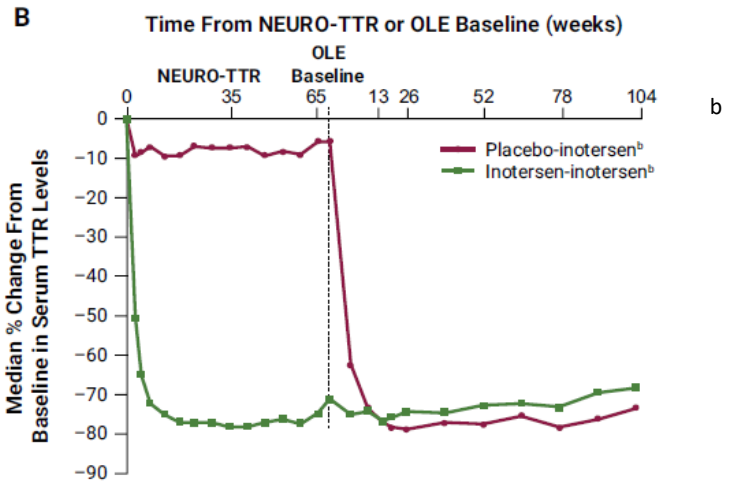
AEs occurring in ≥10% in either group		
Preferred AE term, number of patients (%)	**Placebo (n=77)**	**Patisiran (n=148)**
Diarrhea	29 (38)	55 (37)
Edema, peripheral	17 (22)	**44 (30)**
Fall	**22 (29)**	25 (17)
Nausea	**16 (21)**	22 (15)
IRR	7 (9)	**28 (19)**
Constipation	13 (17)	22 (15)
UTI	**14 (18)**	19 (13)
Dizziness	11 (14)	19 (13)
Fatigue	8 (10)	18 (12)
Headache	9 (12)	16 (11)
Cough	9 (12)	15 (10)
Vomiting	8 (10)	15 (10)
Asthenia	9 (12)	14 (9)
Insomnia	7 (9)	15 (10)
Nasopharyngitis	6 (8)	15 (10)
Pain in extremity	8 (10)	10 (7)
Muscular weakness	**11 (14)**	5 (3)
Anemia	**8 (10)**	3 (2)
Syncope	**8 (10)**	3 (2)

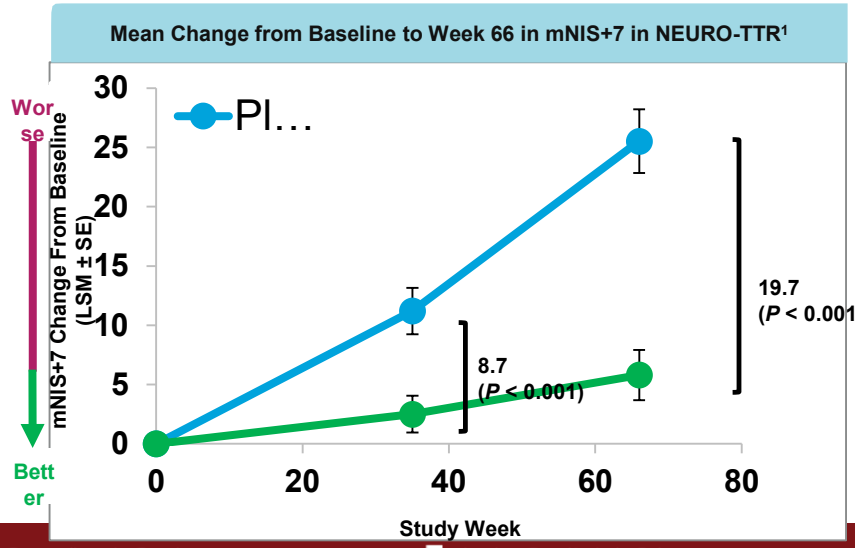
Blue, bolded text: Indicates ≥5 percentage point difference in either group

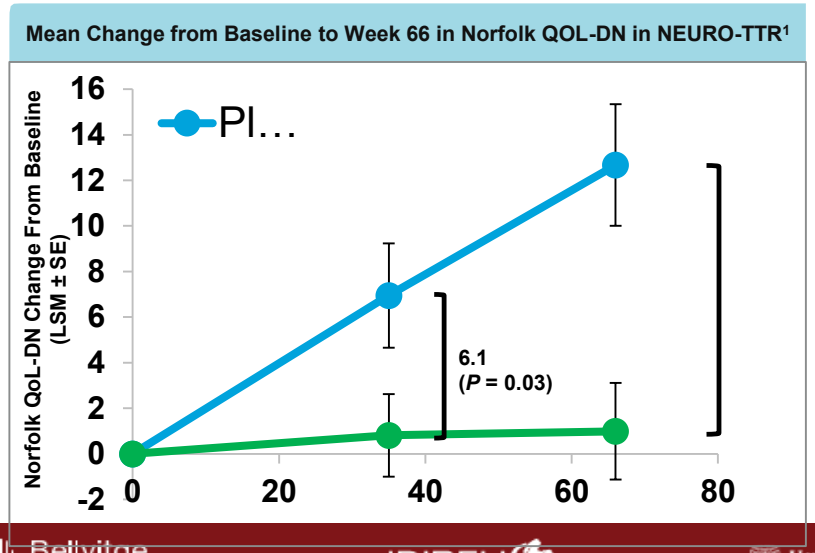
Adams D, et al. N Engl J Med 2018; 379:11-21

Estudio NeuroTTR. Resultados









Platelet and renal monitoring have been effective in the OLE study

- No new safety signals were identified
- There were no new cases of grade 4 platelet count decrease or acute glomerulonephritis
- Few patients (19 [14.1%]) discontinued treatment because of TEAEs
- Serious TEAEs occurred in 47 patients (34.8%) and were considered treatment related in 5 patients (3.7%)
- 9 fatal TEAEs occurred during the OLE; none were considered related to treatment

Most common (≥10%) TEAEs across both groups:

- Nausea, urinary tract infection, vomiting, diarrhea, fatigue, chills, fall, peripheral edema, injection-site pain, thrombocytopenia, syncope, and injection-site erythema, headache, muscular weakness, myalgia, and dyspnea

	Placebo-inotersen n = 50	Inotersen-inotersen n = 85
Treatment exposure during OLE, median (range), days	513.0 (106–1286)	655.0 (1–1429)
Discontinued treatment because of TEAEs, n (%)	4 (8.0)	15 (17.6)
Serious TEAEs, n (%)	14 (28.0)	33 (38.8)
Serious TEAEs considered related to treatment, n (%)	1 (2.0)	5 (3.7)

TEAE, treatment emergent adverse event; OLE, open-label extension.
Brannagan T et al. *Eur J Neurol.* 2020;27(8):1374-1381.

¿Hay lugar todavía para el tafamidis?

JCI insight

Predictive model of response to tafamidis in hereditary ATTR polyneuropathy

Cecília Monteiro, … , Teresa Coelho, Jeffery W. Kelly

JCI Insight. 2019;4(12):e126526. https://doi.org/10.1172/jci.insight.126526.

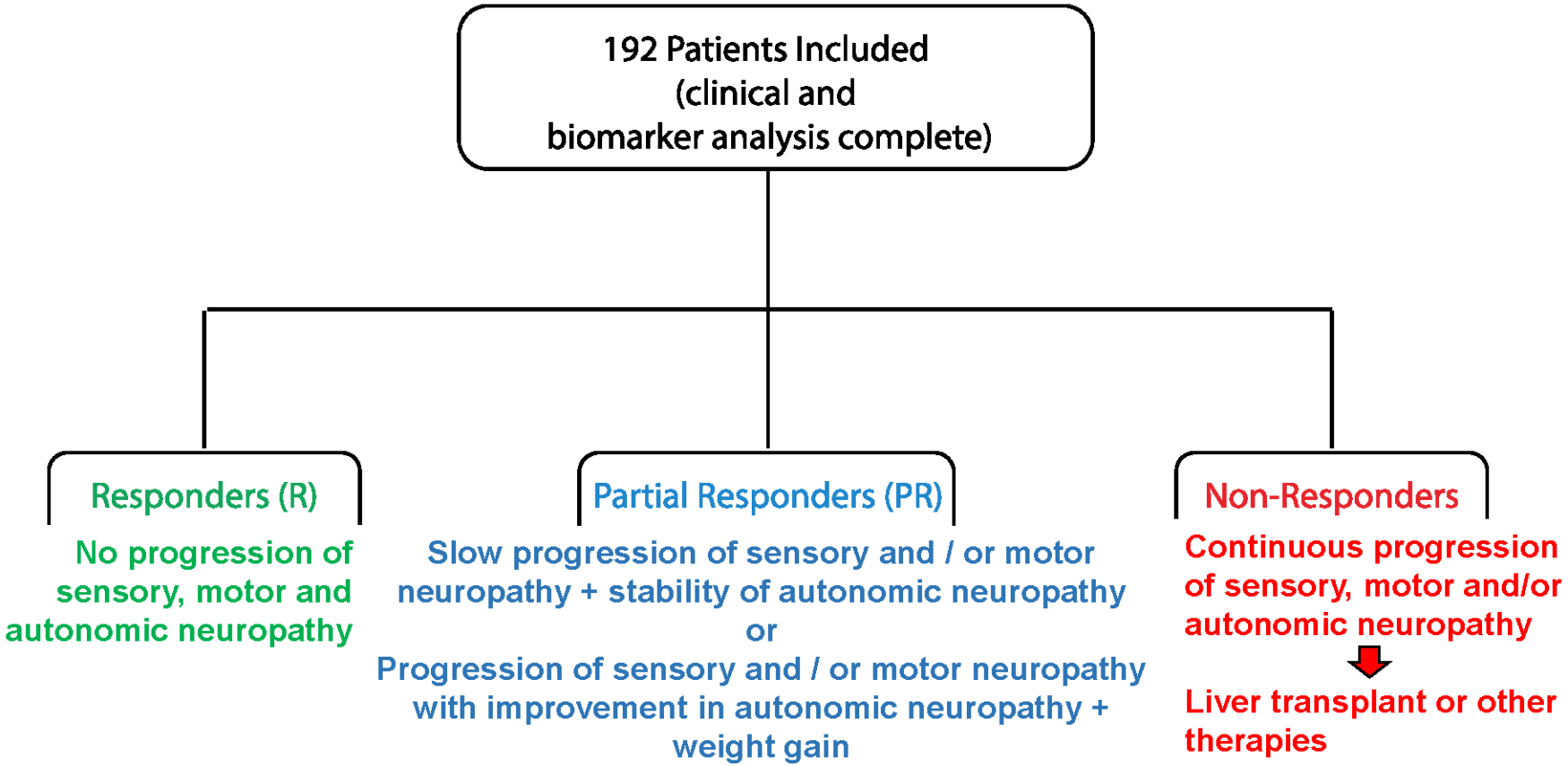
Clinical Medicine | Neuroscience | Therapeutics

The hereditary transthyretin (TTR) amyloidoses are a group of diseases for which several disease-modifying treatments are now available. Long-term effectiveness of these therapies is not yet fully known. Moreover, the existence of alternative therapies has resulted in an urgent need to identify patient characteristics that predict response to each therapy.

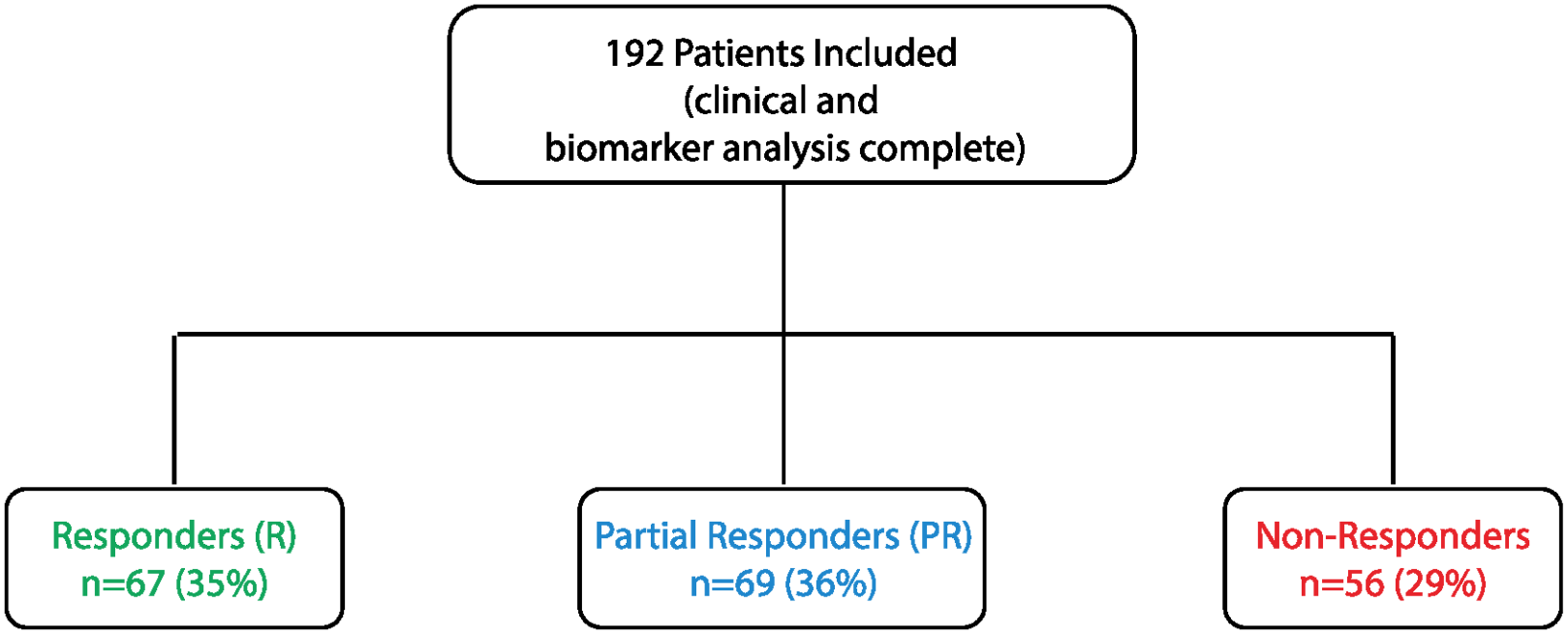
We carried out a retrospective cohort study of 210 patients with hereditary TTR amyloidosis treated with the kinetic stabilizer tafamidis (20 mg qd). These patients were followed for a period of 18–66 months, after which they were classified by an expert as responders, partial responders, or nonresponders. Correlations between baseline demographic and clinical characteristics, as well as plasma biomarkers and response to therapy, were investigated.

34% of patients exhibited an almost complete arrest of disease progression (classified by an expert as responders); 36% had a partial to complete arrest in progression of some but not all disease components (partial responders); whereas the remaining 30% continued progressing despite therapy (nonresponders). We determined that disease severity, sex, and native TTR concentration at the outset of treatment were the most relevant predictors of response to tafamidis. Plasma tafamidis concentration after 12 months […]

Response to Therapy

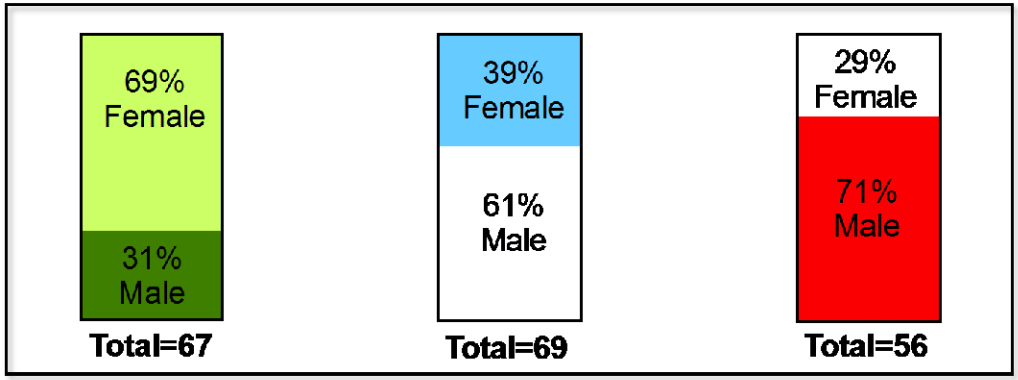


Response to Therapy



Outcome predictors:
Gender Predicts Outcome to Tafamidis

	Responders (R) N=67	Partial Responders (PR) N=69	Non-Responders (NR) N=56	P-value (R vs PR)	P-value (R vs NR)	P-value (PR vs NR)
Female Gender (n, %)	**46 (69%)**	27 (39%)	16 (29%)	**P<0.0001**	**P<0.0001**	ns



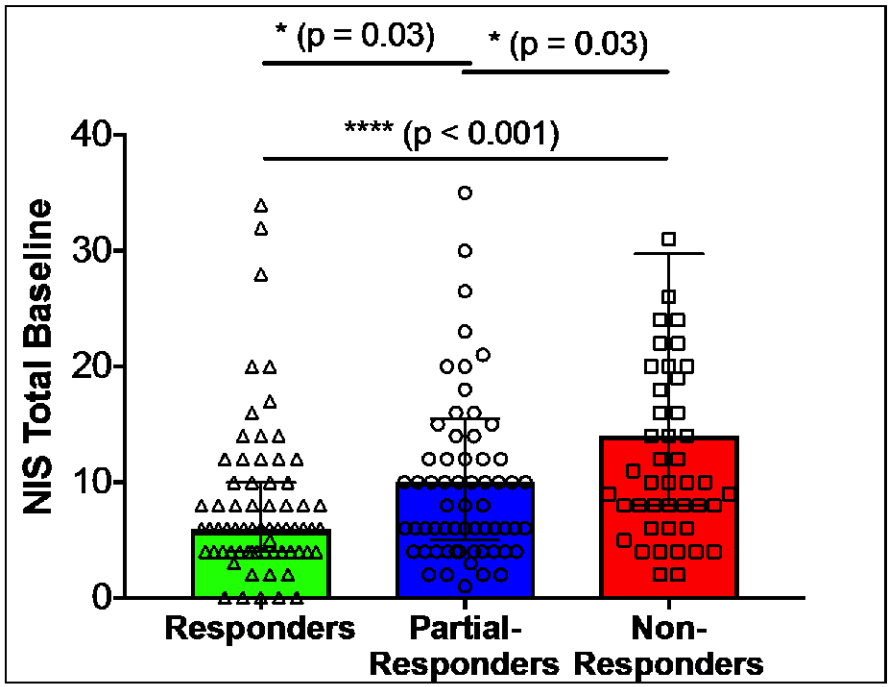
Women are more likely to be **completely stable**

[OR 4.2 (2.1 – 8.3, 95% CI, p<0.0001)]

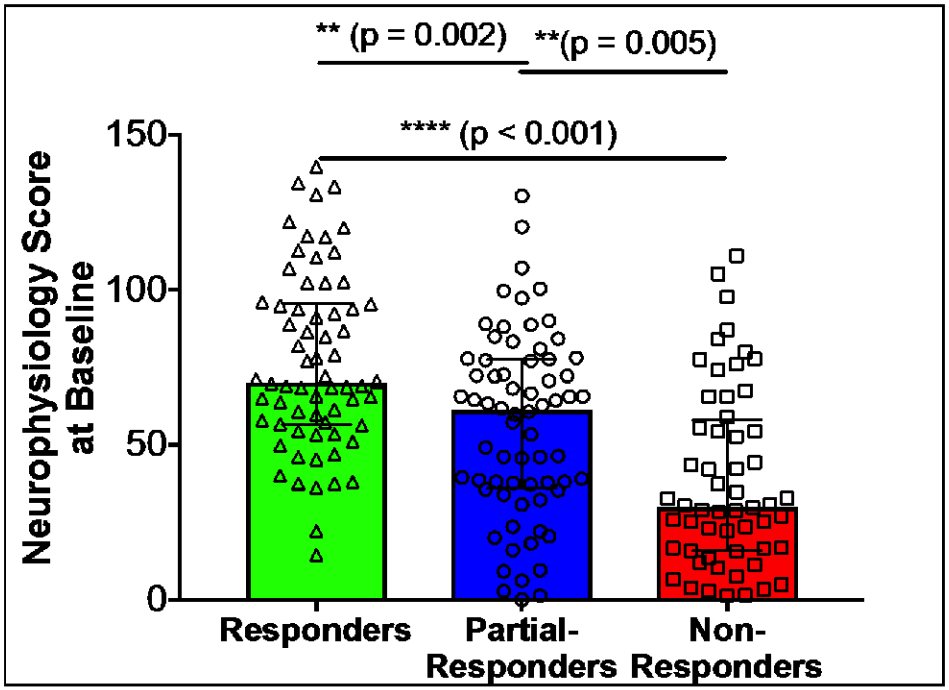
Outcome predictors:

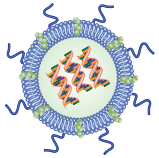
Disease Severity Predicts Outcome to Tafamidis

Neuropathy Impairment Score - Total



Neurophysiology Score





Estudio abierto de patisiran en pacientes con amiloidosis hATTR tras el trasplante de hígado ortotópico (THO)

Patisiran tras el Transplante Hepático Ortotópico

(NCT03862807)

Estudio fase 3 abierto realizado en diversos países europeos

- Edad ≥18 años
- THO por AhTTR **≥12 meses** antes del inicio del estudio
- Empeoramiento de la puntuación PND después de THO[a]
- KPS ≥70%; clase NYHA ≤II
- No tratamiento previo con patisiran o inotersen.
- Ausencia de rechazo del injerto hepático ≤ 6 meses previos

Patisiran 0.3 mg/kg IV cada 3 SEMANAS durante 12 MESES

Objetivo primario: Promedio del porcentaje de reducción de TTR a los 6 y 12 meses

Objetivo secundario:
Cambio a 12 meses en:
- NIS
- Norfolk QOL-DN
- R-ODS
- COMPASS-31
- IMCm

Seguridad (frecuencia de EA)

Describir los resultados provisionales de eficacia y seguridad a los 6 meses en pacientes inscritos con amiloidosis hATTR con polineuropatía con progresión de la enfermedad después de TOH

[a]Ya sea en comparación con la evaluación previa al TOH o entre 2 evaluaciones posteriores al TOH.
EA, episodios adversos; COMPASS-31, Composite Autonomic Symptom Score 31-item questionnaire; KPS, Karnofsky Performance Status; mBMI, modified body mass index; NIS, Neuropathy Impairment Score; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; NYHA, New York Heart Association; OLT, orthotopic liver transplantation; PND, polyneuropathy disability; q3w, every 3 weeks; R-ODS, Rasch-Built Overall Disability Scale; TTR, transthyretin

Datos demográficos (n=23)

Características basales	
Edad media (rango)	58,0 (43,0–76,0)
Hombres (%)	13,0 (56,5)
País (%)	
España	7 (30,4)
Francia	5 (21,7)
Alemania	3 (13,0)
Portugal	3 (13,0)
Italia	2 (8,7)
Suecia	2 (8,7)
Reino Unido	1 (4,3)
Edad media al momento del diagnóstico de amiloidosis hATTR (DE)	46.7 (11,7)
Genotipo Val30Met[a] (%)	15.0 (65,2)
Edad media en el momento del trasplante (DE)	49.7 (10,9)
Tiempo medio desde el diagnóstico hasta THO[b] (DE)	3.8 (3,1)
Tiempo medio desde el THO hasta la primera dosis de patisiran[b] (DE)	9.4 (5,2)
Media del IMC[c], kg/m^2 (DE)	23.5 (3,6)
Nivel basal sérico medio de TTR, mg/L (rango)	202,1 (123,7–315,1)
Media NIS (rango)	60,2 (7,0–136,5)

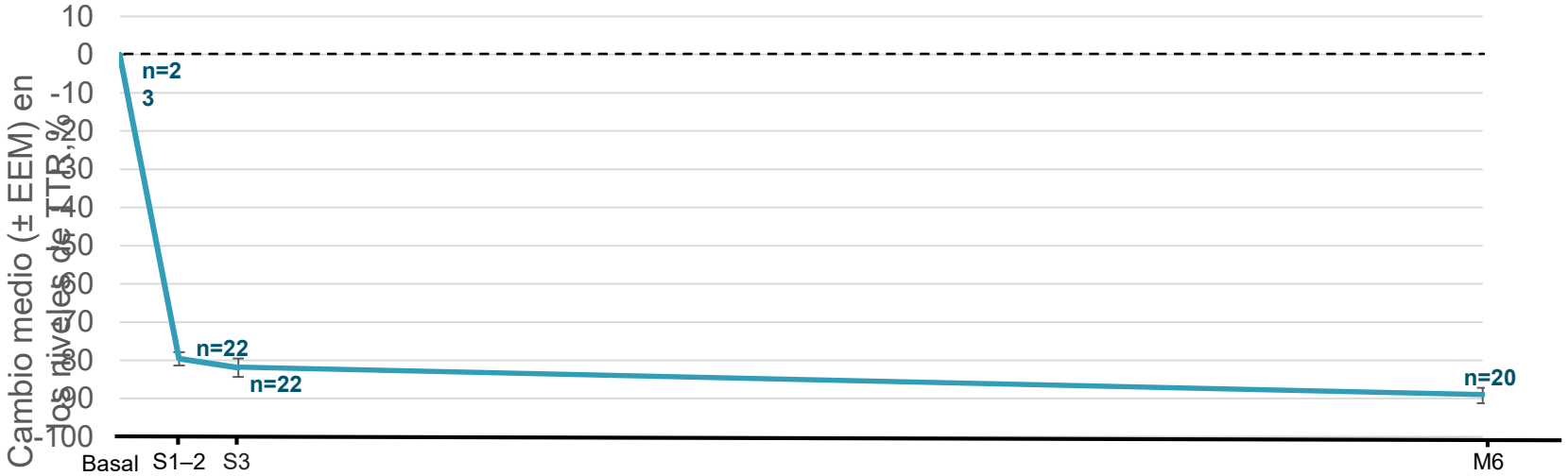
IMC, índice de masa corporal; NIS, Neuropathy Impairment Score; TOH, trasplante ortotópico de hígado; DE, desviación estándar; TTR, transtiretina.
[a]Otros genotipos incluidos: G47A, G47V, L12V, F64L, S77Y, y Y116S. [b]n=22. [c]n=21; faltan los datos de 2 pacientes porque faltan los datos de su altura en la visita de cribado

Los pacientes se sometieron a THO un promedio de 3,8 años después del diagnóstico.

En promedio, los pacientes recibieron su **primera dosis de patisiran > 9 años después del THO**

Reducción rápida y duradera de los niveles séricos de TTR en el tratamiento con patisirán

Después de 6 meses de tratamiento con patisiran, la reducción media en los niveles séricos basales de TTR fue del **89,2%.**



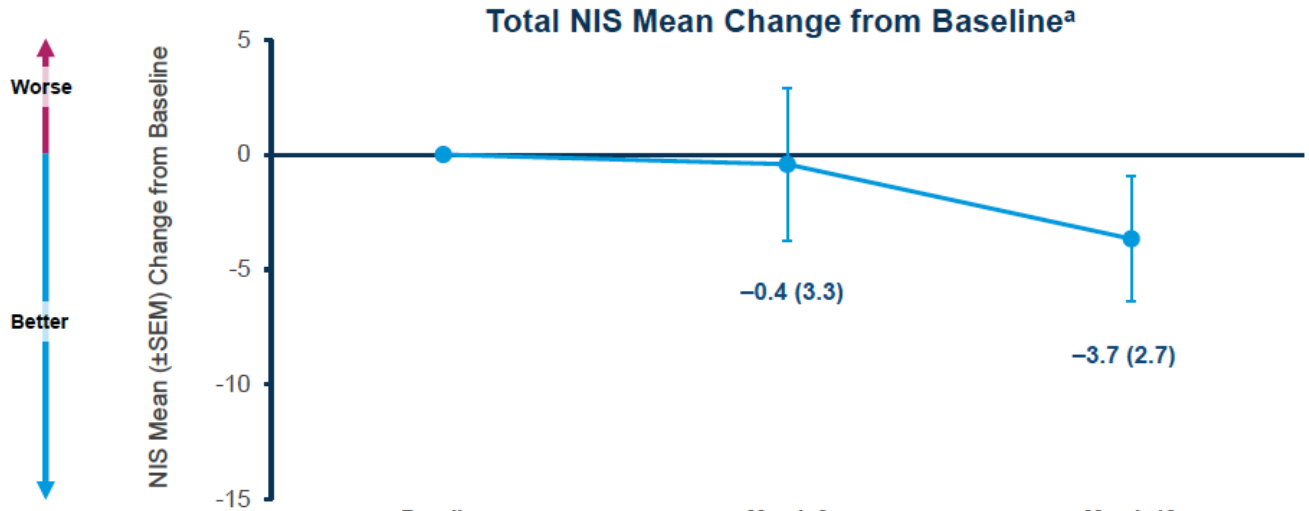
	Basal	S1–2	S3	M6
Nivéles séricos TTR, mg/L (DE)	202.1 (54,1)	41.1 (19,4)	35.5 (21,2)	21,2 (16,6)

THO, trasplante ortotópico hepático; DE, desviación estándar; EEM, error estándar de la media; TTR,transtiretina; Sem, semana

Improvement in Neuropathy with Patisiran

Secondary Endpoint

- At Month 12, there was an **improvement** in neuropathy, as demonstrated by a decrease in the mean total NIS score from baseline



	Baseline	Month 6	Month 12
n	21	20	20
Mean (±SEM)	60.0 (8.9)	58.6 (9.1)	55.3 (10.1)
Mean change from baseline (±SEM)	–	–0.4 (3.3)	–3.7 (2.7)

[a]Data for the per protocol analysis set shown. Twenty-one patients were included in the per protocol analysis set (meeting the criteria of ≤2 missing doses due to COVID-19)

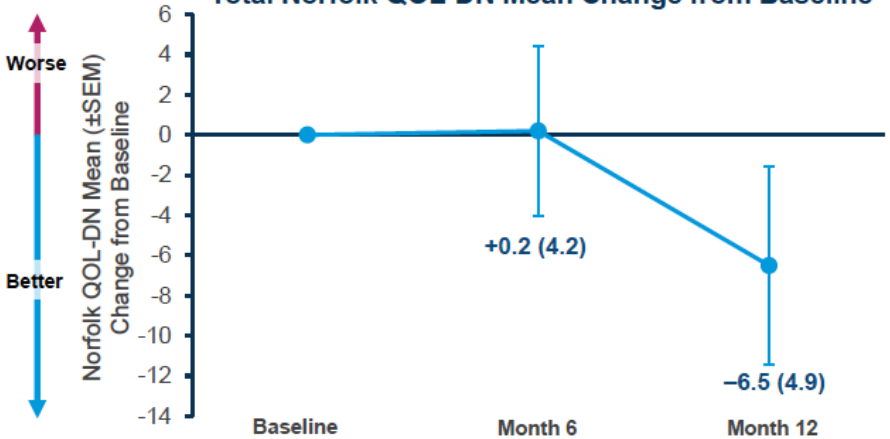
NIS, Neuropathy Impairment Score; SEM, standard error of the mean

Improvement in QOL and Autonomic Symptoms with Patisiran

Secondary Endpoints

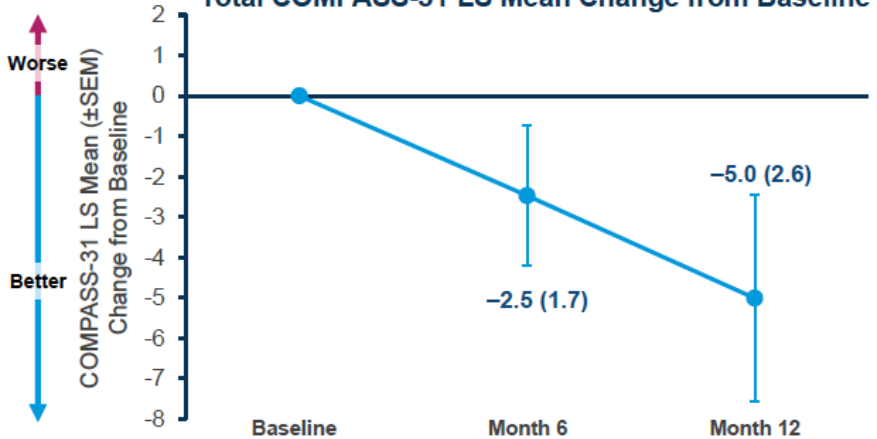
- At Month 12, there was an **improvement** in QOL (decrease in mean total Norfolk QOL-DN score) and autonomic symptoms (decrease in LS mean total COMPASS-31 score) from baseline

Total Norfolk QOL-DN Mean Change from Baseline[a]



	Baseline	Month 6	Month 12
n	21	20	21
Mean (±SEM)	65.4 (5.5)	65.3 (6.3)	59.0 (6.3)
Mean (±SEM) change from baseline	–	+0.2 (4.2)	–6.5 (4.9)

Total COMPASS-31 LS Mean Change from Baseline[a]



	Baseline	Month 6	Month 12
n	20	20	21
Mean (±SEM)	37.4 (3.7)	37.1 (3.9)	34.2 (3.9)
n	20	19	20
LS mean (±SEM) change from baseline	–	–2.5 (1.7)	–5.0 (2.6)

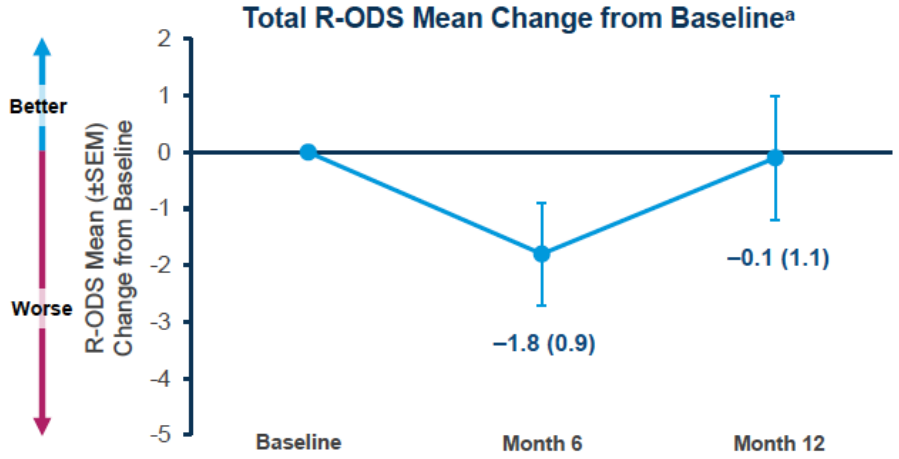
[a]Data for the per protocol analysis set shown. Twenty-one patients were included in the per protocol analysis set (meeting the criteria of ≤2 missing doses due to COVID-19)

COMPASS-31, Composite Autonomic Symptom Score 31-item questionnaire; LS, least squares; Norfolk QOL-DN, Norfolk Quality of Life-Diabetic Neuropathy questionnaire; QOL, quality of life; SEM, standard error of the mean

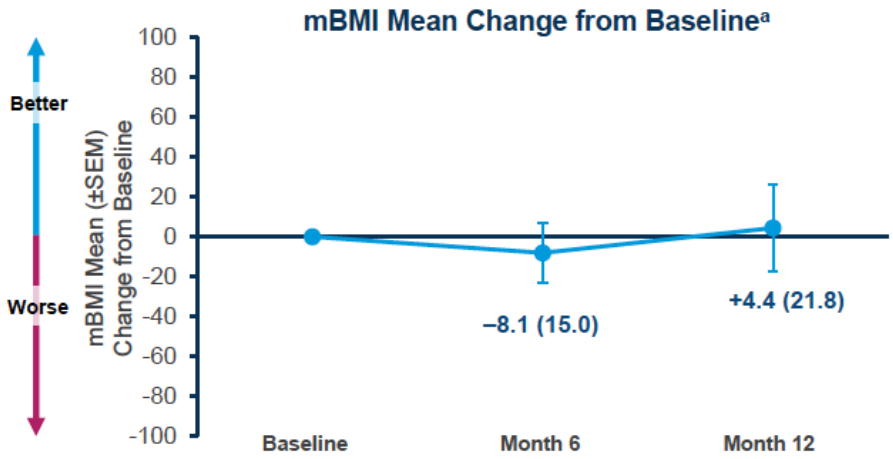
Stabilization in Disability and Nutritional Status with Patisiran

Secondary Endpoints

- Through 12 months, the measures of disability (total R-ODS) and nutritional status (mBMI) were **stable** relative to baseline



	Baseline	Month 6	Month 12
n	21	20	21
Mean (±SEM)	29.1 (1.8)	27.2 (2.5)	29.0 (2.4)
Mean (±SEM) change from baseline	–	–1.8 (0.9)	–0.1 (1.1)



	Baseline	Month 6	Month 12
n	21	20	21
Mean (±SEM)	929.9 (29.7)	931.5 (32.4)	934.3 (28.1)
Mean (±SEM) change from baseline	–	–8.1 (15.0)	+4.4 (21.8)

[a]Data for the per protocol analysis set shown. Twenty-one patients were included in the per protocol analysis set (meeting the criteria of ≤2 missing doses due to COVID-19)
mBMI, modified body mass index; R-ODS, Rasch-built Overall Disability Scale; SEM, standard error of the mean

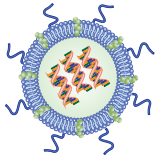
Resumen de seguridad, análisis preliminar [a]

Paciente con episodio, n (%)	Pacientes que recibieron patisiran (n=23)
EA	23 (100,0)
EA observados en ≥10% de los pacientes	
Diarrea	8 (34,8)
Edema periférico	5 (21,7)
Dolor de espalda	5 (21,7)
Reacción relacionada con la infusión	4 (17,4)
Infección del tracto urinario	3 (13,0)
Fatiga	3 (13,0)
EA relacionados con el fármaco del estudio	5 (21,7)
EAG relacionado con el fármaco del estudio	1 (4,3)
EA que condujo a la interrupción de la administración del medicamento	8 (34,8)
EA que condujo a abandonar el estudio	0
Muerte	0

La mayoría de los EA fueron leves o moderados y consistentes con el estudio APOLLO[1]

- EA más común relacionado con el tratamiento: RRI (4 pacientes, 17,4%)
- 6 EAG: Rotura de cadera, insuficiencia cardíaca (2 pacientes), colangitis, rechazo del trasplante, RRI; únicamente 1 se consideró como relacionado con el fármaco del estudio (RRI)

  Rechazo del trasplante probablemente debido a inmunosupresión insuficiente, biopsia hepática 15ª post-THO compatible; el paciente continuó bajo tratamiento con el fármaco del estudio
- Trastornos hepáticos leves y transitorios (<3 × LSN) en 7 (30,4%) pacientes, La función hepática se mantuvo estable en la mayoría de los pacientes.

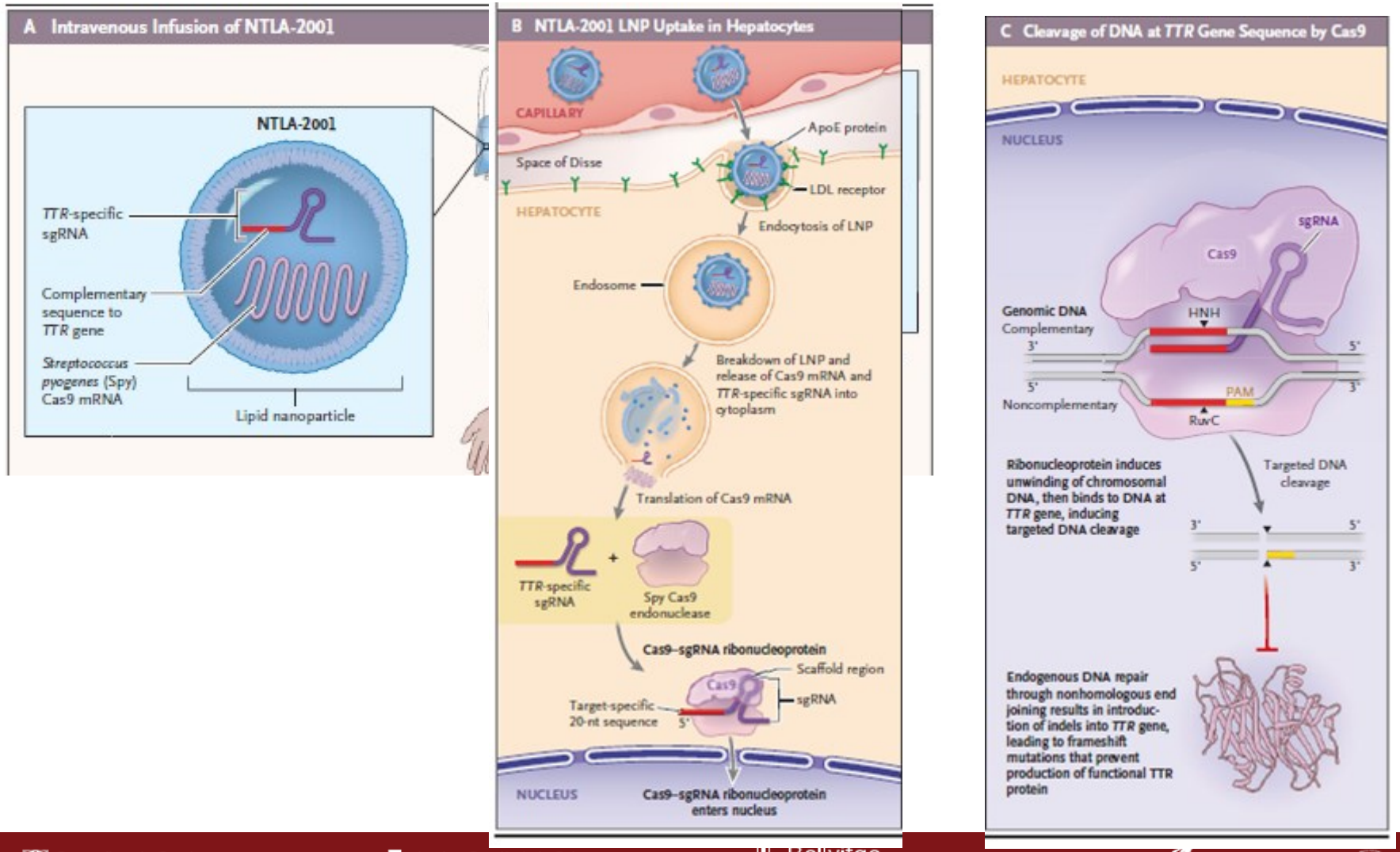


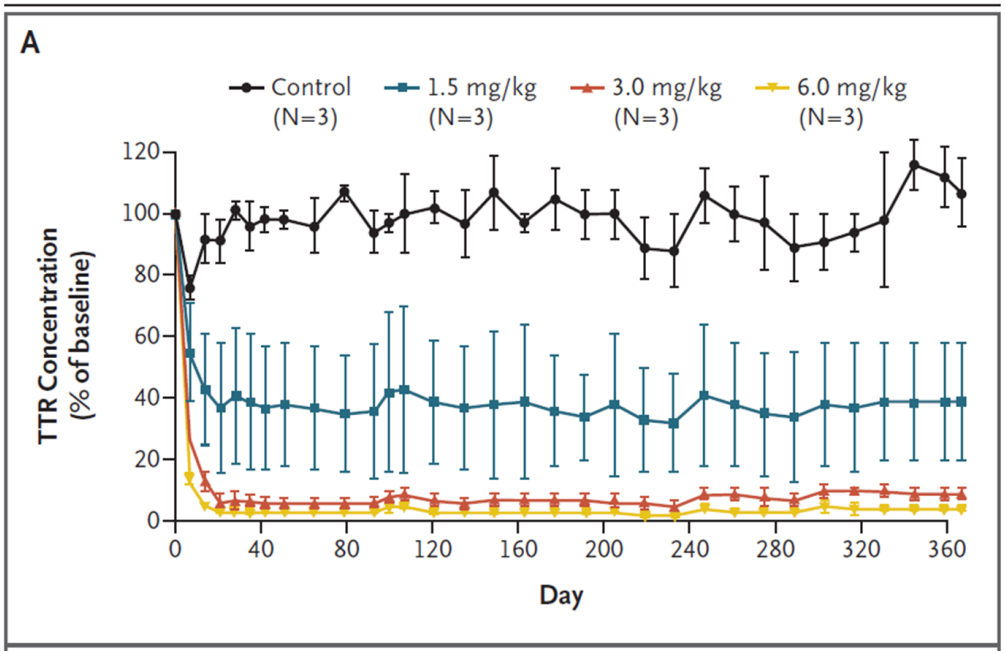
Estudio de Patisiran después de DLT (CCP-PAT-2020-01) Estudio POSTAUTORIZACIÓN abierto (EPA01420) de la AEMPS

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 5, 2021 VOL. 385 NO. 6

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis




A
Control (N=3)
1.5 mg/kg (N=3)
3.0 mg/kg (N=3)
6.0 mg/kg (N=3)
TTR Concentration (% of baseline)
120
100
80
60
40
20
0
0
40
80
120
160
200
240
280
320
360
Day

Manejo Multidiciplinar

Internista
Neurólogo
Cardiólogo
Digestólogo
Oftalmólogo
Unidad de Transplante Cardíaco/Hepático

Conclusión

- Enfermedad tratable
- Múltiples opciones
  - Estabilizadores TTR
  - RNAi (ASO/SiRNA)
  - Sintomático
  - Manejo multidisciplinar
  - THO/TC
  - Tratamiento de post OLT y post DLT
  - Y lo que falta por venir…


UNIVERSITAT DE BARCELONA
IDIBELL
Institut d'Investigació Biomèdica de Bellvitge
Bellvitge
Hospital Universitari