II Jornada de l'Estratègia de Malalties Minoritàries de les Illes Balears.
Actualització en Malalties Minoritàries

Govern de les Illes Balears
Conselleria de Salut

Avances terapéuticos en Amiloidosis ATTRv:

Juan González-Moreno

UM-ATTR. Medicina Interna

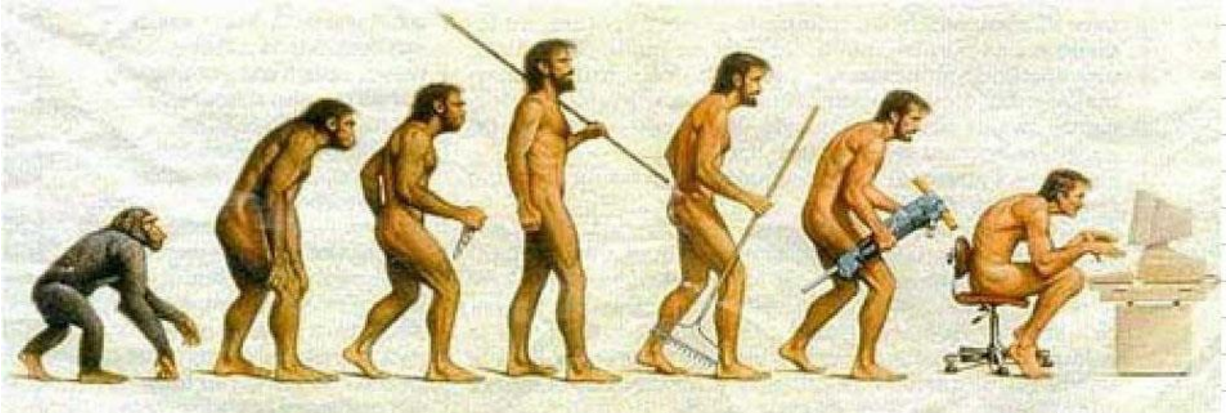
ATTR HUSLL

Institut d'Investigació Sanitària Illes Balears
IdISBa

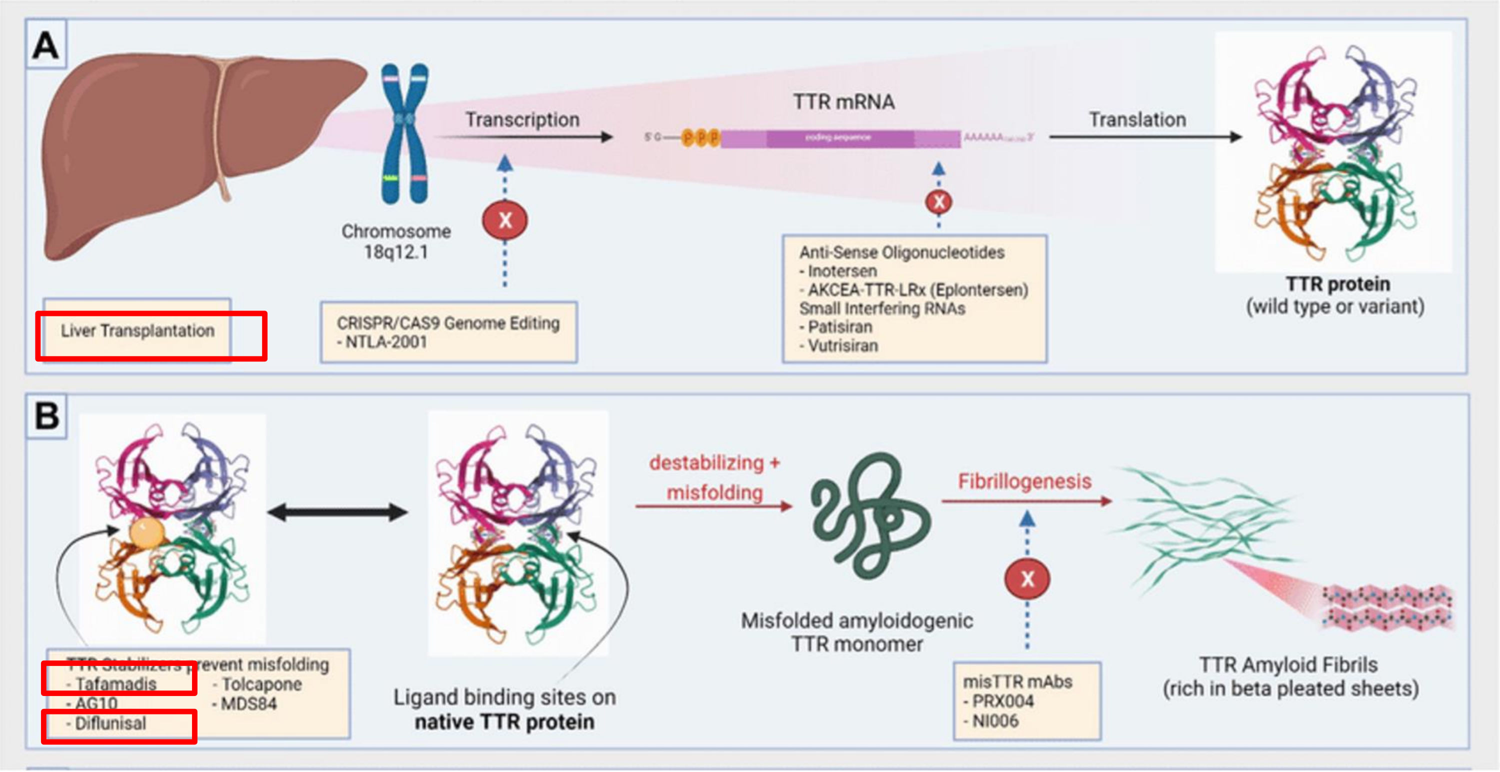
SON LLÀTZER
HOSPITAL UNIVERSITARI

INDICE

- ¿De dónde venimos?
- ¿Dónde estamos?
- ¿A dónde vamos?



¿DE DÓNDE VENIMOS?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Chromosome 18q12.1
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TTR mRNA
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CRISPR/CAS9 Genome Editing
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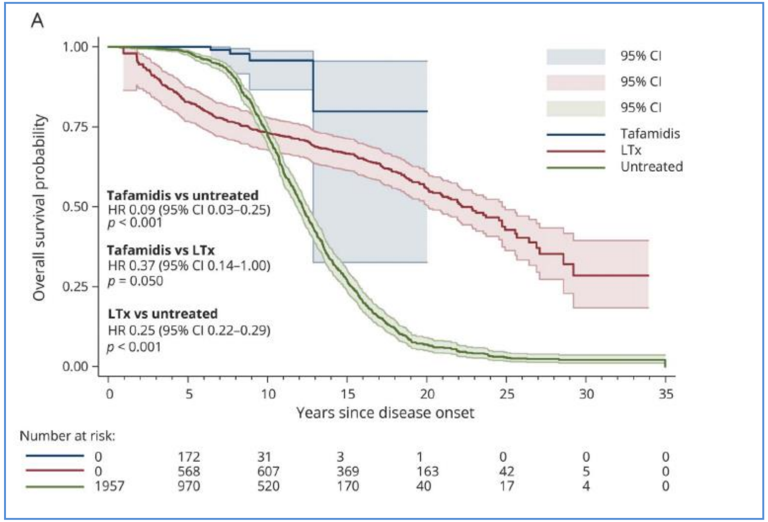
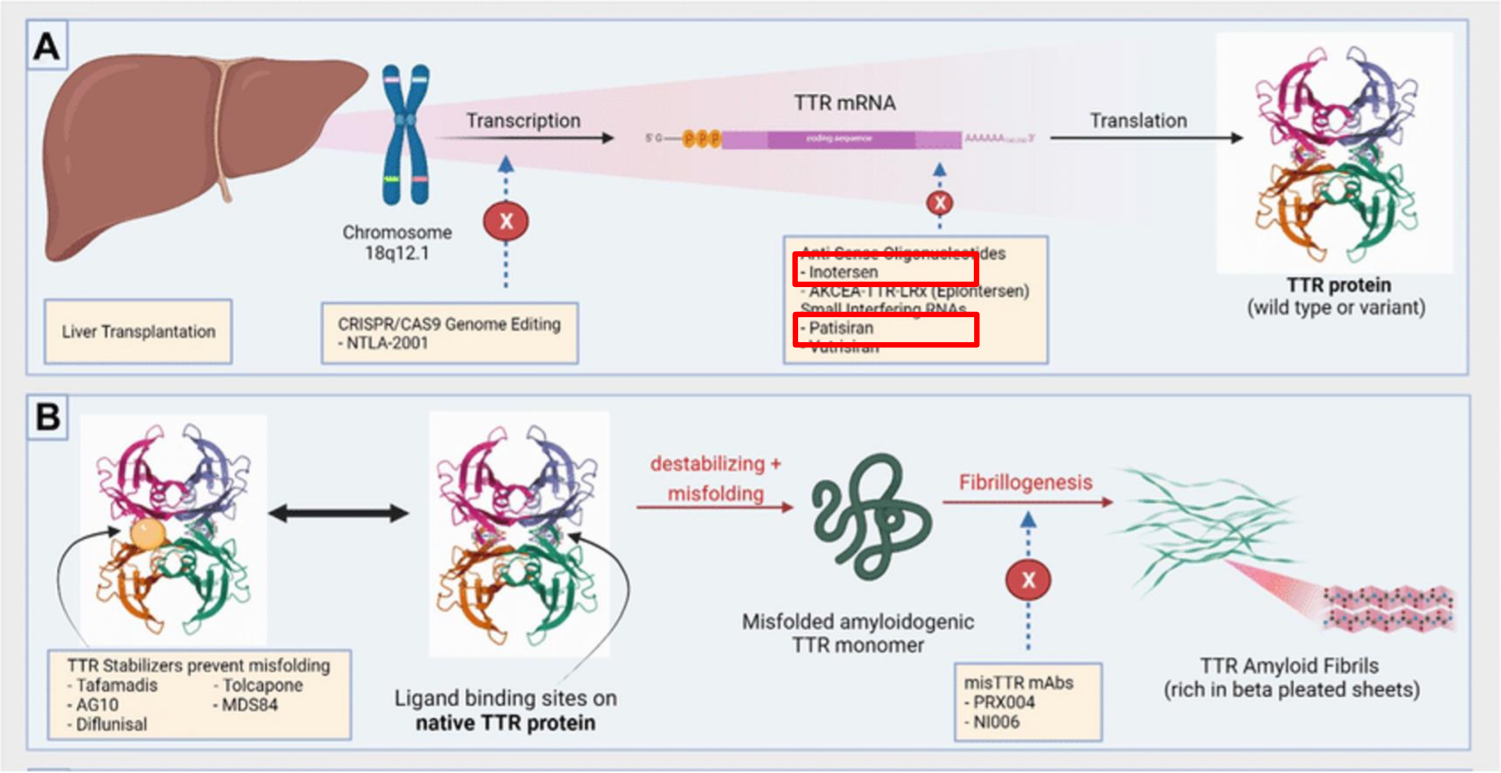
- Inotersen
- AKCEA-TTR-LRx (Eplontersen)
Small Interfering RNAs
- Patisiran
- Vutrisiran
B
destabilizing +
misfolding
Fibrillogenesis
Misfolded amyloidogenic
TTR monomer
TTR Amyloid Fibrils
(rich in beta pleated sheets)
TTR Stabilizers prevent misfolding
- Tafamadis
- AG10
- Diflunisal
- Tolcapone
- MDS84
Ligand binding sites on
native TTR protein
misTTR mAbs
- PRX004
- NI006

Primeros pasos

- Años 90: trasplante hepático.
- Diflunisal: "Off-label"
- 2011: Tafamidis 20 mg (ATTR-PN)



Coelho T, et al. Neurology. 2018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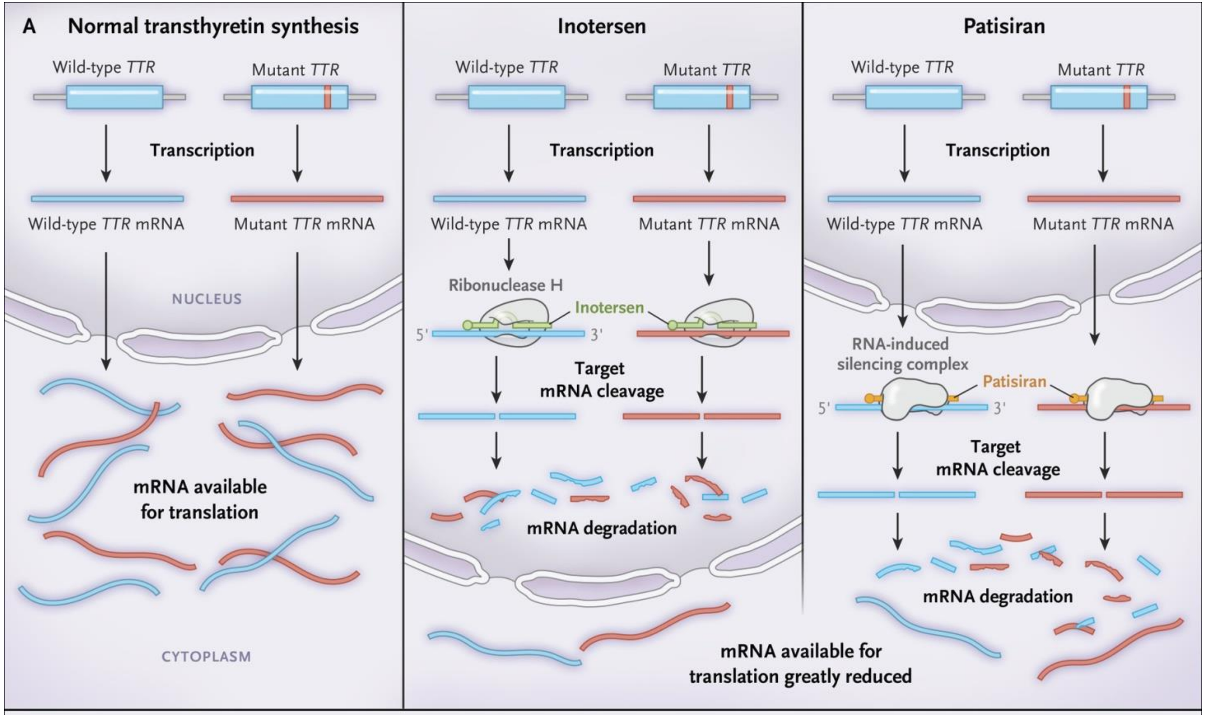
2018: Silenciadores génicos



Buxbaum JN. N Engl J Med. 2018.

Hasta "ayer"

ATTRv - Polineuropatía

Estadío I

↓

TAFAMIDIS
20 mg oral
diario

Si se objetiva progresión

↓

PATISIRAN
0.3mg/Kg IV
c/3 semanas

o

INOTERSEN
284 mg SC
c/1 semana

Estadío II

↓

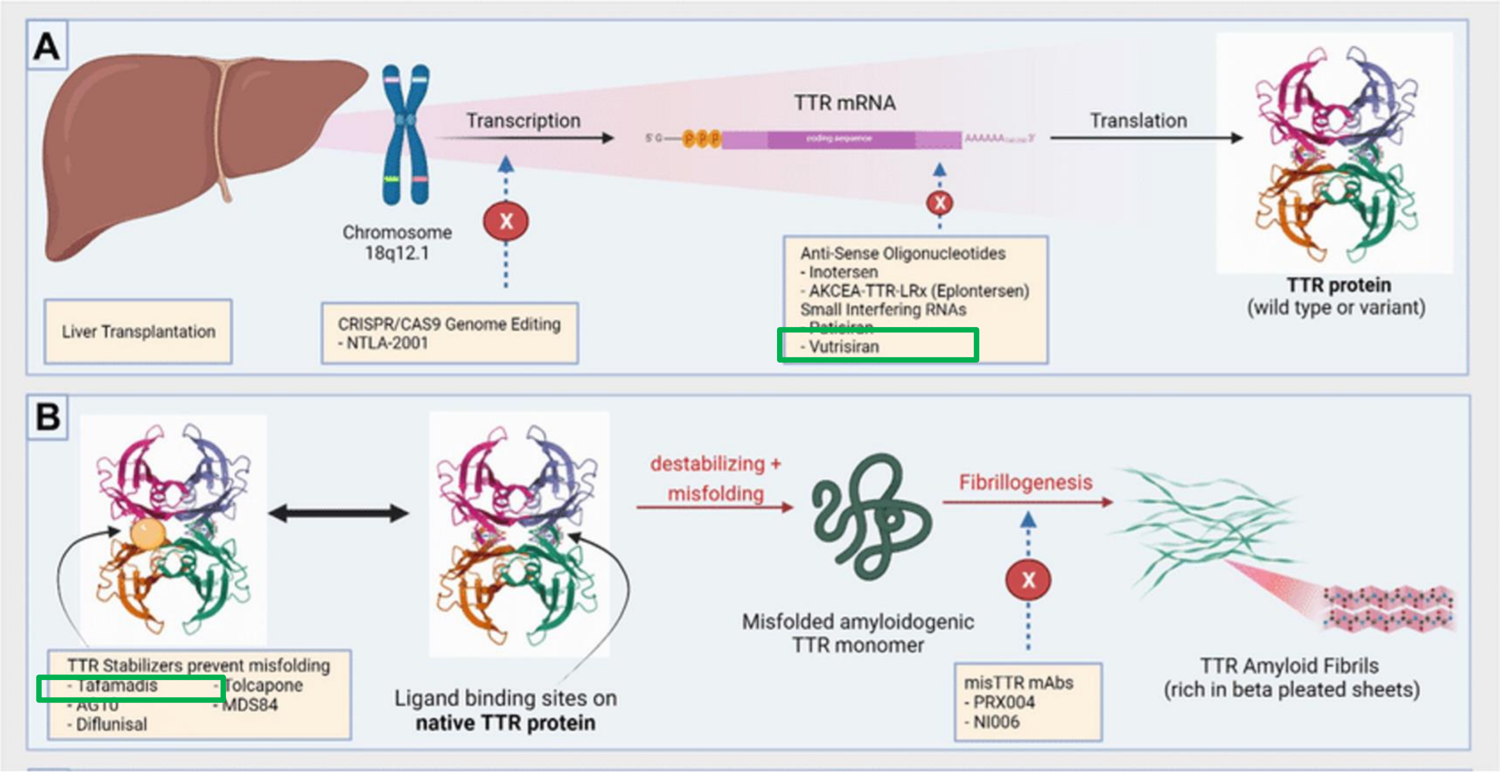
PATISIRAN
0.3mg/Kg IV
c/3 semanas

o

INOTERSEN
284 mg SC
c/1 semana

El trasplante hepático se reservará para los pacientes refractarios a los tratamientos propuestos o por decisión unilateral por su parte.

¿DÓNDE ESTAMOS?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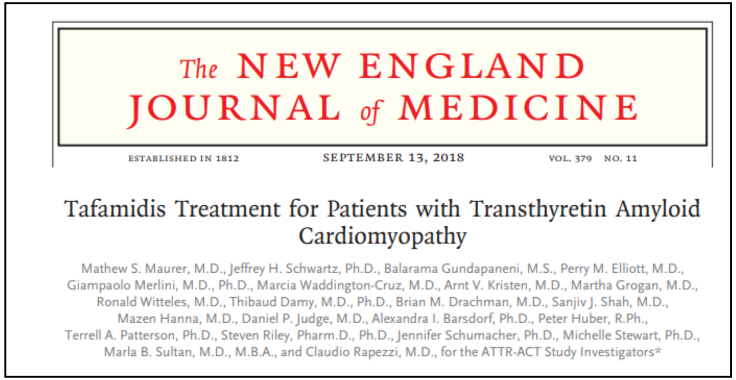
Tafamidis 61mg

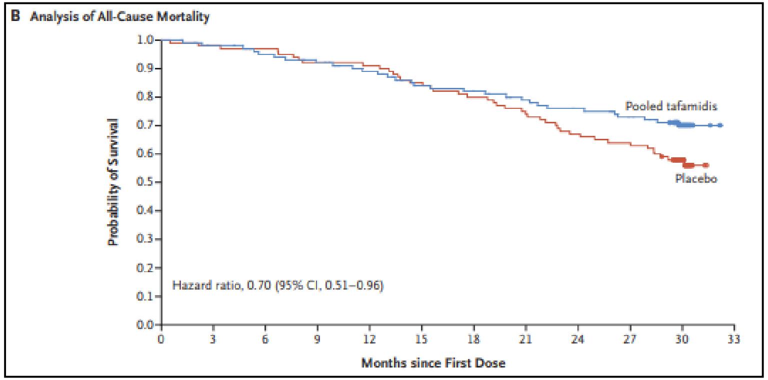
1 comprimido oral diario

- Indicación para ATTR(v o wt)-Cardiomiopatía.
- Financiado en España desde 06/2023.
- Ensayo pivotal: ATTR-ACT


The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 SEPTEMBER 13, 2018 VOL. 379 NO. 11

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

Mathew S. Maurer, M.D., Jeffrey H. Schwartz, Ph.D., Balarama Gundapaneni, M.S., Perry M. Elliott, M.D., Giampaolo Merlini, M.D., Ph.D., Marcia Waddington-Cruz, M.D., Arnt V. Kristen, M.D., Martha Grogan, M.D., Ronald Witteles, M.D., Thibaud Damy, M.D., Ph.D., Brian M. Drachman, M.D., Sanjiv J. Shah, M.D., Mazen Hanna, M.D., Daniel P. Judge, M.D., Alexandra I. Barsdorf, Ph.D., Peter Huber, R.Ph., Terrell A. Patterson, Ph.D., Steven Riley, Pharm.D., Ph.D., Jennifer Schumacher, Ph.D., Michelle Stewart, Ph.D., Marla B. Sultan, M.D., M.B.A., and Claudio Rapezzi, M.D., for the ATTR-ACT Study Investigators*



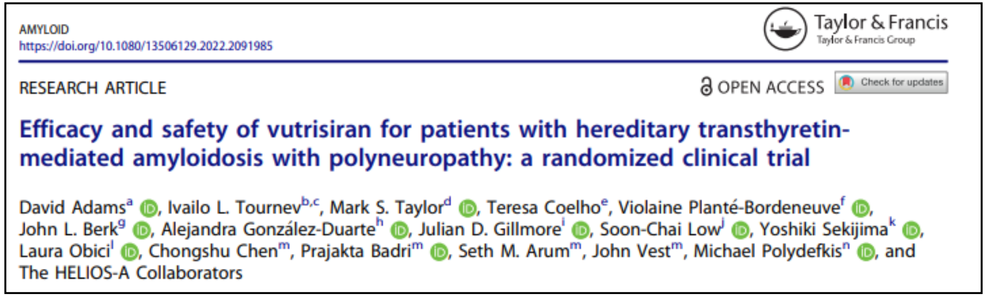
Tafamidis 61mg

– Eficaz para reducir la mortalidad incluso en edades avanzadas (>80años). (Sarkar et al, 2024; Garcia-Pavia et al, 2024)
– Eficaz también en estadios avanzados (NYHA III). (Elliot et al, 2023)
– Mantiene resultados de eficacia a largo plazo (60 meses). (Gorram et al, 2024)
– Eficaz tanto en FEVI preservada como disminuida. (Shah et al, 2024)

Vutrisiran

1 inyección SC
cada 3 meses

- Indicación para ATTRv-polineuropatía.
- Financiado en España desde 09/2023.
- Ensayo pivotal: HELIOS-A.

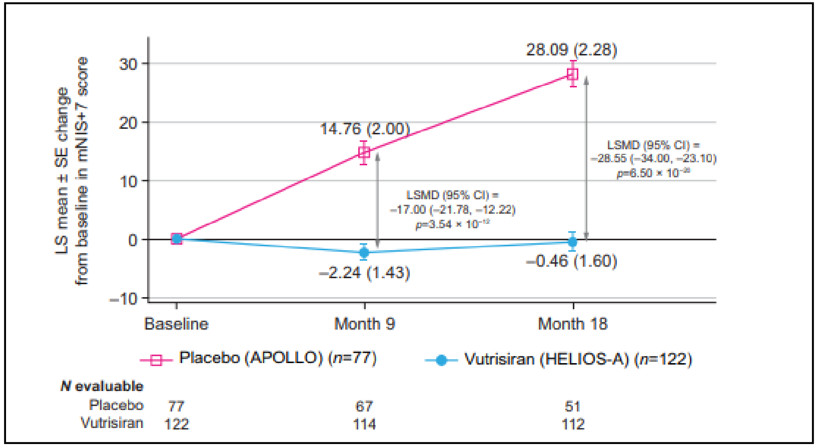

AMYLOID
https://doi.org/10.1080/13506129.2022.2091985
Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

OPEN ACCESS | Check for updates

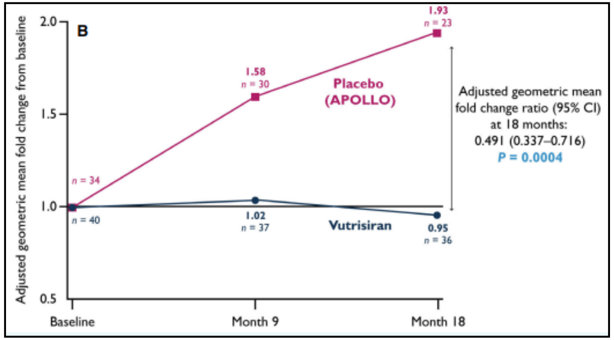
Efficacy and safety of vutrisiran for patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy: a randomized clinical trial

David Adams[a], Ivailo L. Tournev[b,c], Mark S. Taylor[d], Teresa Coelho[e], Violaine Planté-Bordeneuve[f], John L. Berk[g], Alejandra González-Duarte[h], Julian D. Gillmore[i], Soon-Chai Low[j], Yoshiki Sekijima[k], Laura Obici[l], Chongshu Chen[m], Prajakta Badri[m], Seth M. Arum[m], John Vest[m], Michael Polydefkis[n], and The HELIOS-A Collaborators

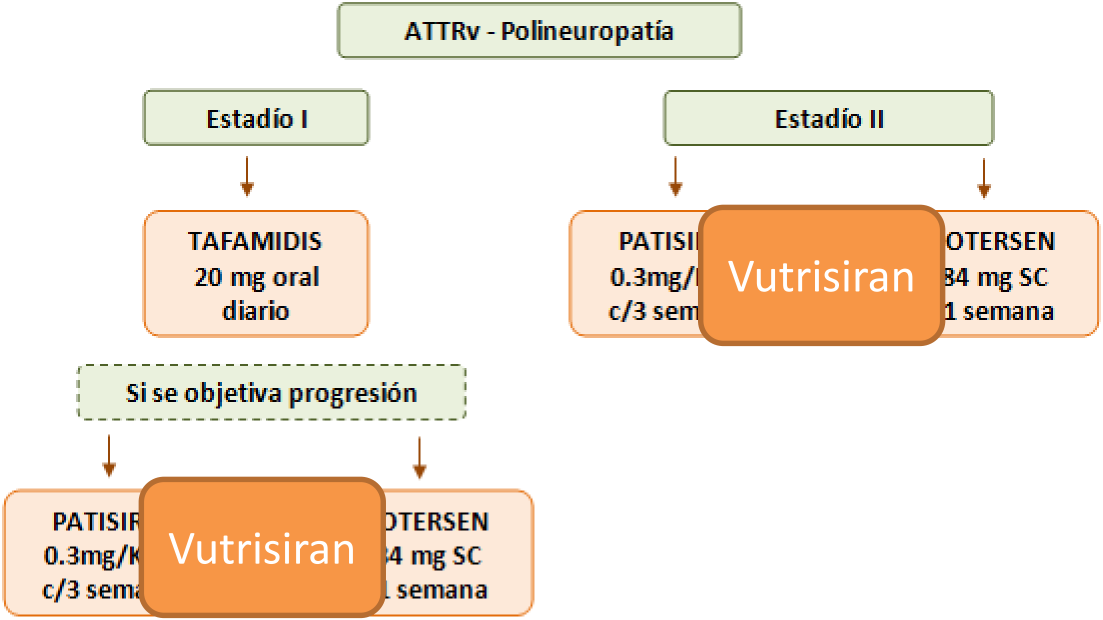


Vutrisiran

- Además, dos subestudios:
  - Parámetros exploratorios NTproBNP y ETT en HELIOS-A favorecen a vutrisiran. (García-Pavia et al, 2024)
  - Mejoría en calidad de vida y función física. (Obici et al, 2023)



Hoy



El trasplante hepático se reservará para los pacientes refractarios a los tratamientos propuestos o por decisión unilateral por su parte.

Hoy

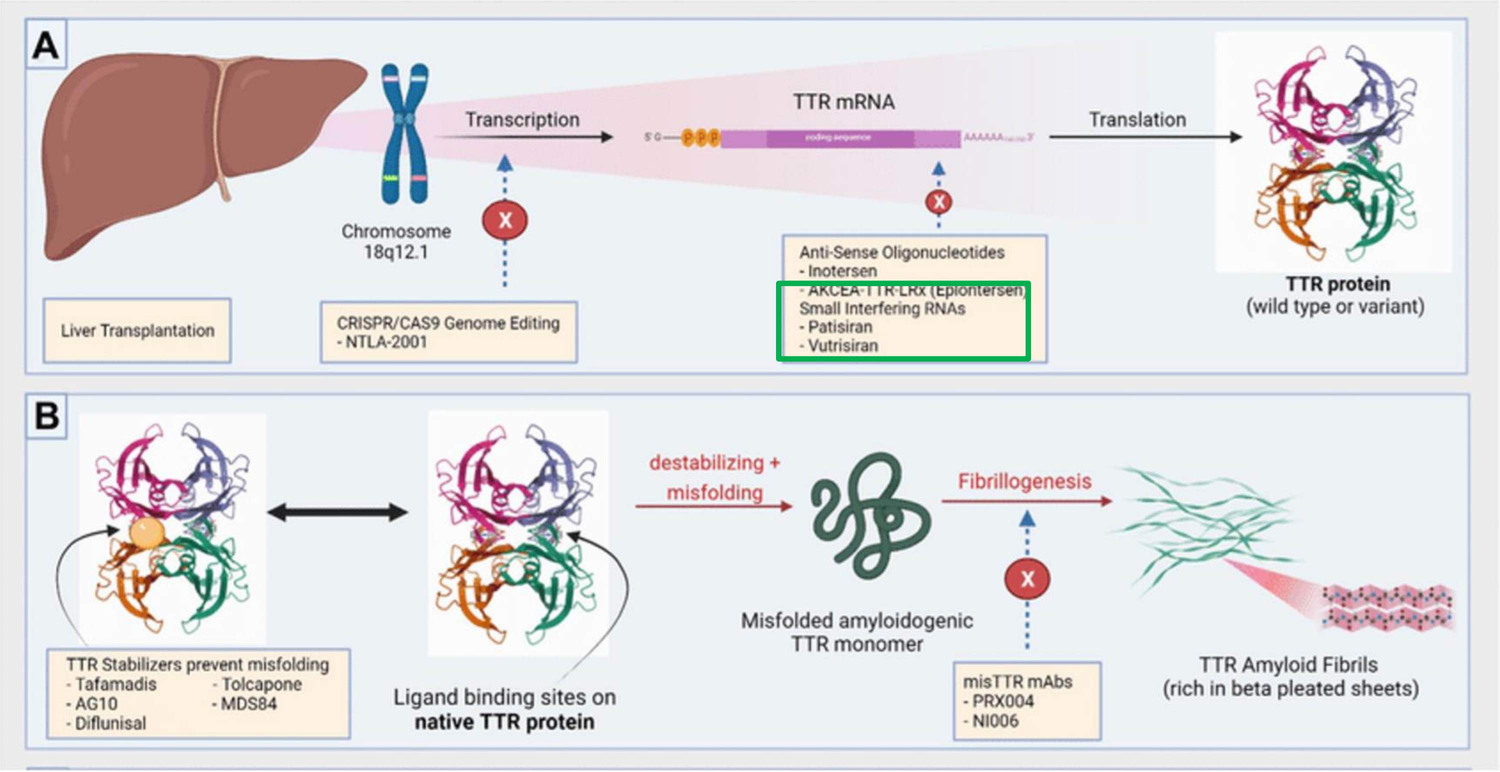
ATTR HUSLL

ATTR-cardiomiopatía

Tafamidis 61mg oral diario

En pacientes con fenotipo mixto, se deben utilizar los protocolos de ATTR-polineuropatía

¿A DÓNDE VAMOS?



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(rich in beta pleated sheets)

Patisiran

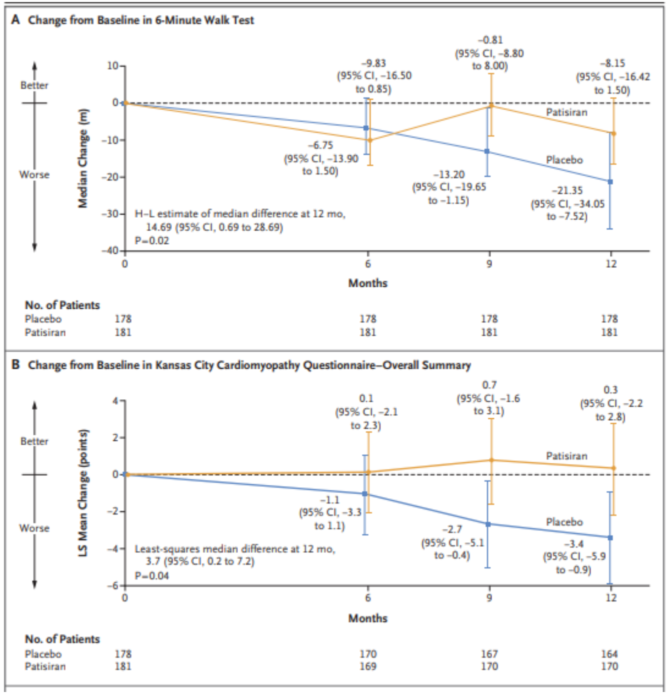
- Ensayo pivotal en ATTR-CM: APOLLO-B

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 26, 2023 VOL. 389 NO. 17

Patisiran Treatment in Patients with Transthyretin Cardiac Amyloidosis

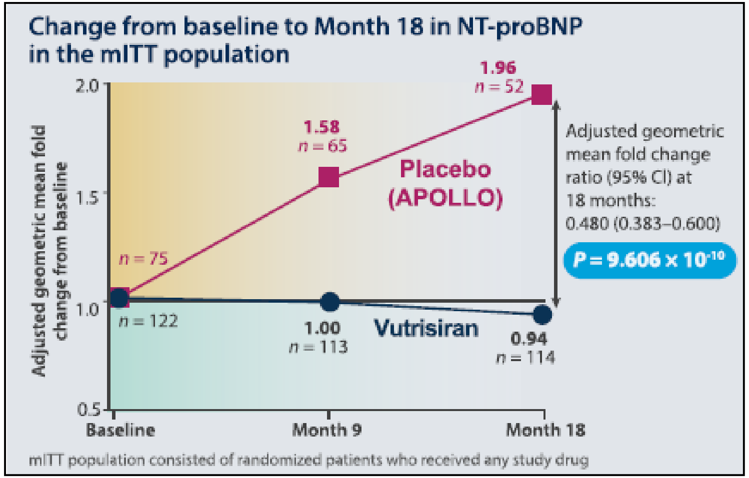
M.S. Maurer, P. Kale, M. Fontana, J.L. Berk, M. Grogan, F. Gustafsson, R.R. Hung, R.L. Gottlieb, T. Damy, A. González-Duarte, N. Sarswat, Y. Sekijima, N. Tahara, M.S. Taylor, M. Kubanek, E. Donal, T. Palecek, K. Tsujita, W.H.W. Tang, W.-C. Yu, L. Obici, M. Simões, F. Fernandes, S.H. Poulsen, I. Diemberger, F. Perfetto, S.D. Solomon, M. Di Carli, P. Badri, M.T. White, J. Chen, E. Yureneva, M.T. Sweetser, P.Y. Jay, P.P. Garg, J. Vest, and J.D. Gillmore, for the APOLLO-B Trial Investigators*



Vutrisiran

Impact of vutrisiran on exploratory cardiac parameters in hereditary transthyretin-mediated amyloidosis with polyneuropathy

Pablo Garcia-Pavia[1,2,3]*, Martha Grogan[4], Parag Kale[5], John L. Berk[6], Mathew S. Maurer[7], Isabel Conceição[8], Marcelo Di Carli[9], Scott D. Solomon[10], Chongshu Chen[11], Elena Yureneva[11], John Vest[11], and Julian D. Gillmore[12]



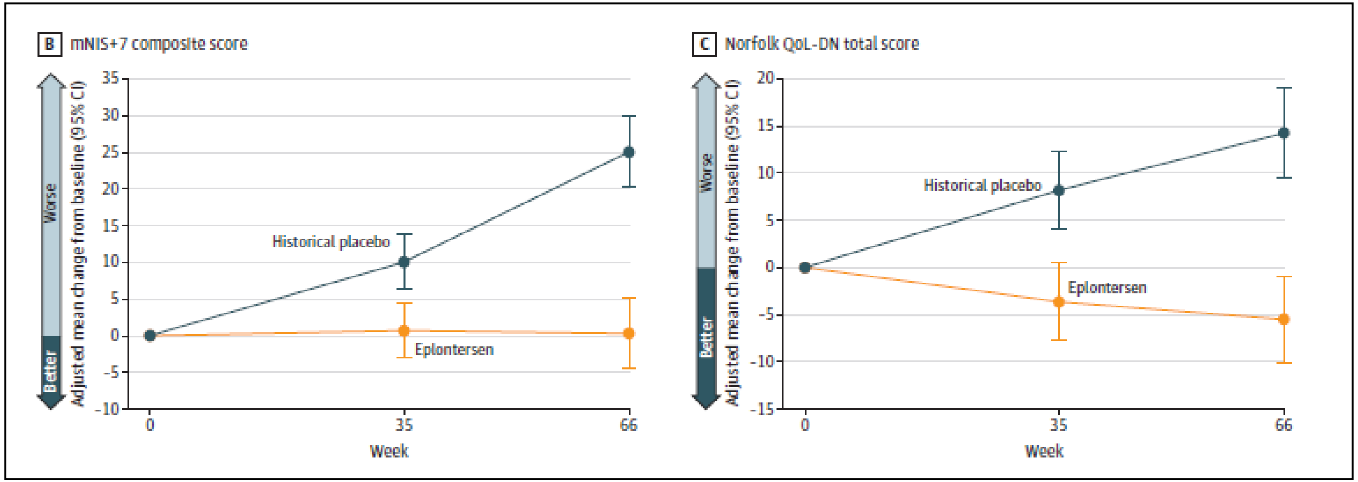
Eplontersen

JAMA | Original Investigation

Eplontersen for Hereditary Transthyretin Amyloidosis With Polyneuropathy

Teresa Coelho, MD, PhD; Wilson Marques Jr, MD, PhD; Noel R. Dasgupta, MD; Chi-Chao Chao, MD, PhD;
Yeşim Parman, MD; Marcondes Cavalcante França Jr, MD, PhD; Yuh-Cherng Guo, MD; Jonas Wixner, MD, PhD;
Long-Sun Ro, PhD; Cristian R. Calandra, MD; Pedro A. Kowacs, MD; John L. Berk, MD; Laura Obici, MD;
Fabio A. Barroso, MD; Markus Weiler, MD; Isabel Conceição, MD; Shiangtung W. Jung, PhD; Gustavo Buchele, PhD;
Michela Brambatti, MD; Jersey Chen, MD, MPH; Steven G. Hughes, MBBS; Eugene Schneider, MD;
Nicholas J. Viney, BSc; Ahmad Masri, MD; Morie R. Gertz, MD; Yukio Ando, MD; Julian D. Gillmore, PhD;
Sami Khella, MD; P. James B. Dyck, MD; Márcia Waddington Cruz, PhD; for the NEURO-TTRansform Investigators

JAMA. 2023;330(15):1448-1458. doi:10.1001/jama.2023.18688



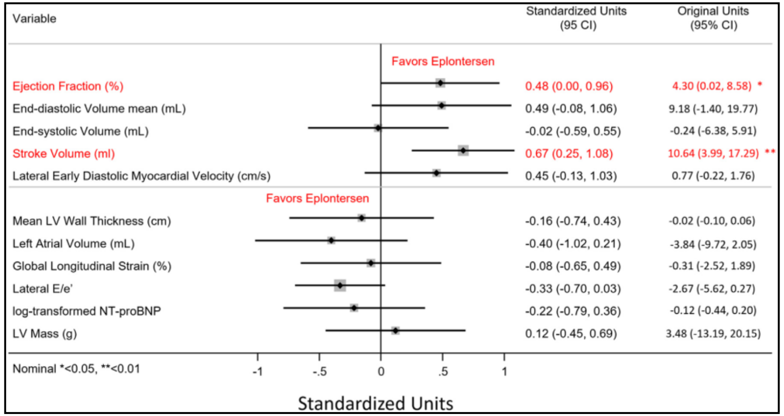
Eplontersen

Journal of Cardiac Failure 00 (2023) 1–8

JCF
Journal of Cardiac Failure

Effect of Eplontersen on Cardiac Structure and Function in Patients With Hereditary Transthyretin Amyloidosis

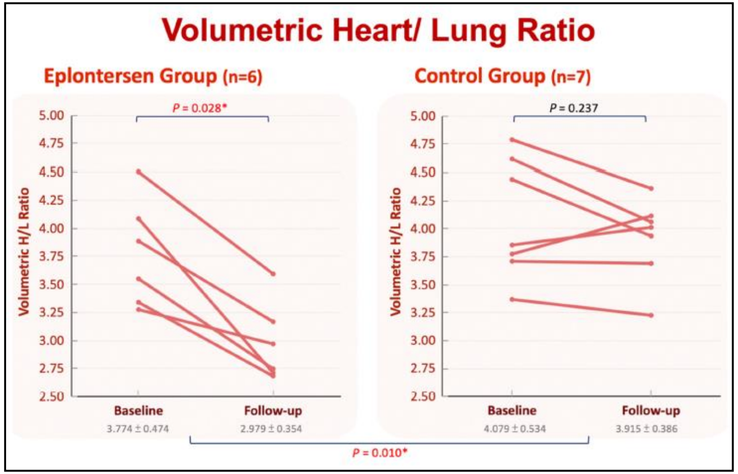
Ahmad Masri[1] Mathew S. Maurer[2] Brian L. Claggett[3] Ian Kulac[3] Marcia Waddington Cruz[4] Isabel Conceição[5] Markus Weiler[6] John L. Berk[7] Morie Gertz[8] Julian D. Gillmore[9] Stephen Rush[10] Jersey Chen[11] Wunan Zhou[11] Jesse Kwoh[12] Jason M. Duran[12] Sotirios Tsimikas[12,13] and Scott D. Solomon[3]

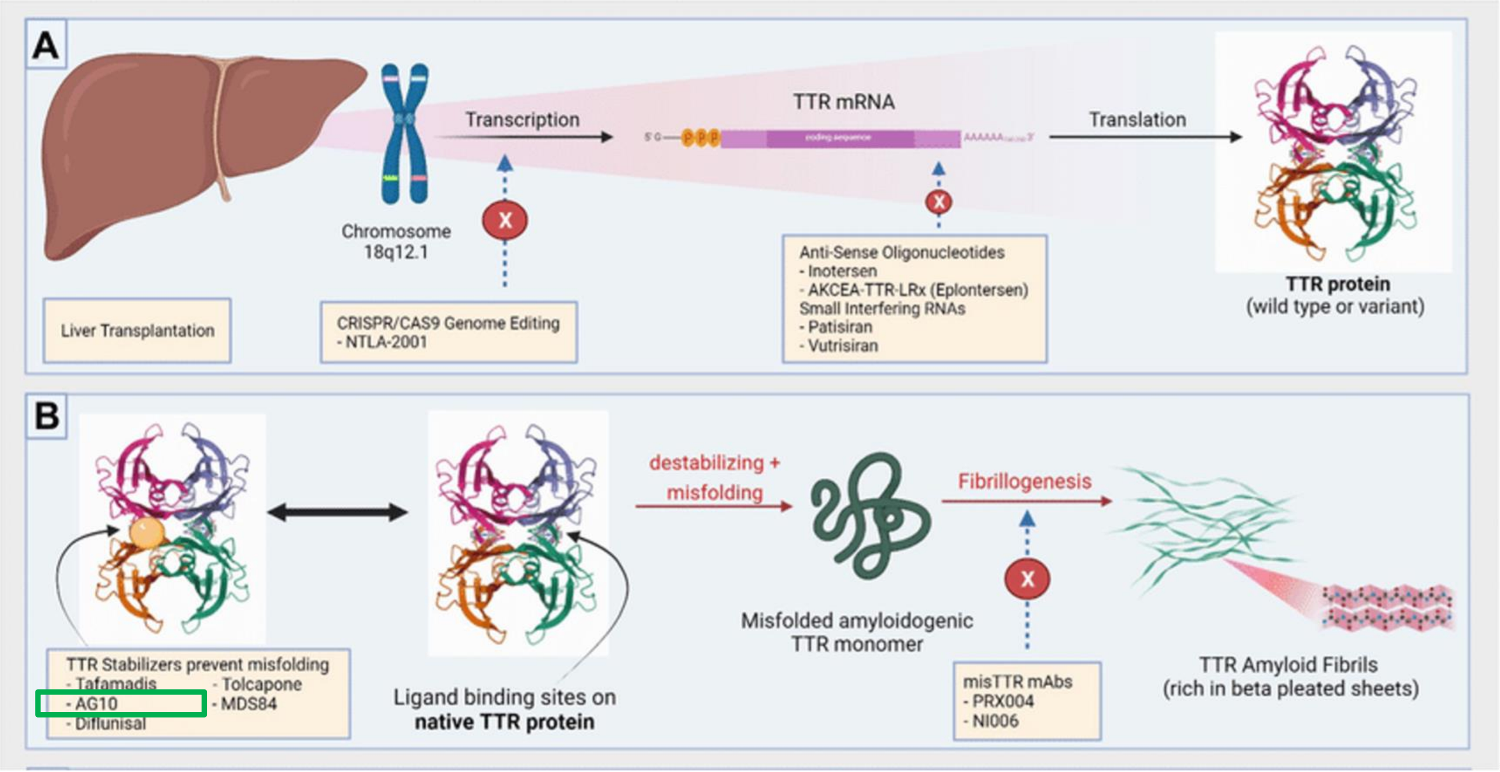


Use of Technetium-99m-Pyrophosphate Single-Photon Emission Computed Tomography/Computed Tomography in Monitoring Therapeutic Changes of Eplontersen in Patients With Hereditary Transthyretin Amyloid Cardiomyopathy

An-Li Yu, MD; Yi-Chieh Chen, MSc; Cheng-Hsuan Tsai, MD; Yuan-Kun Aden Wu, MD; Mao-Yuan Su, PhD; Chia-Hung Chou, PhD; Chia-Tung Shun, MD, PhD; Hsueh-Wen Hsueh, MD, MMS; Jimmy Jyh-Ming Juang, MD, PhD; Ming-Jen Lee, MD, PhD; Ping-Huei Tseng, MD, PhD; Chia-Hua Hsu, MSc; Sung-Tsang Hsieh, MD, PhD; Chi-Lun Ko, MD; Mei-Fang Cheng, MD*; Chi-Chao Chao, MD, PhD*; Yen-Hung Lin, MD, PhD

J Am Heart Assoc. 2024;13:e030512.





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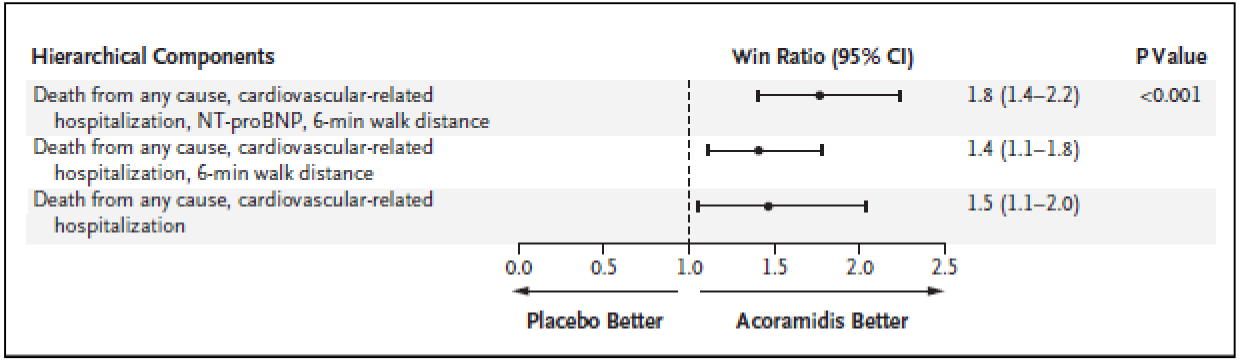
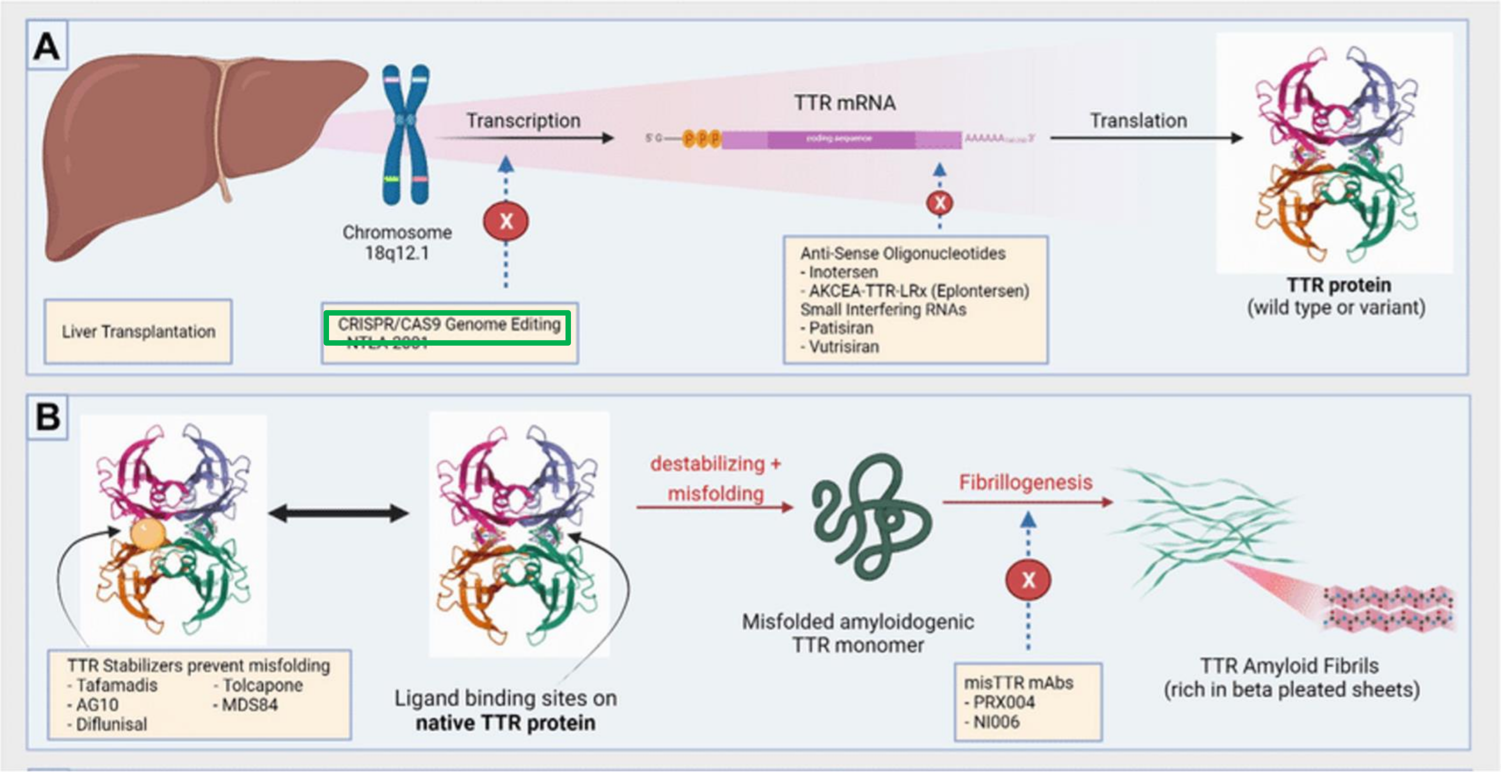
Acoramidis

Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy

J.D. Gillmore, D.P. Judge, F. Cappelli, M. Fontana, P. Garcia-Pavia, S. Gibbs, M. Grogan, M. Hanna, J. Hoffman, A. Masri, M.S. Maurer, J. Nativi-Nicolau, L. Obici, S.H. Poulsen, F. Rockhold, K.B. Shah, P. Soman, J. Garg, K. Chiswell, H. Xu, X. Cao, T. Lystig, U. Sinha, and J.C. Fox, for the ATTRibute-CM Investigators*

N ENGL J MED 390;2 NEJM.ORG JANUARY 11, 2024





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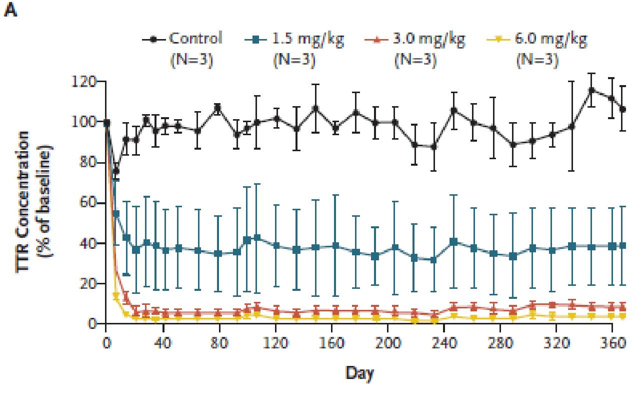
CRISPR

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

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

Julian D. Gillmore, M.D., Ph.D., Ed Gane, M.B., Ch.B., Jorg Taubel, M.D., Justin Kao, M.B., Ch.B., Marianna Fontana, M.D., Ph.D., Michael L. Maitland, M.D., Ph.D., Jessica Seitzer, B.S., Daniel O'Connell, Ph.D., Kathryn R. Walsh, Ph.D., Kristy Wood, Ph.D., Jonathan Phillips, Ph.D., Yuanxin Xu, M.D., Ph.D., Adam Amaral, B.A., Adam P. Boyd, Ph.D., Jeffrey E. Cehelsky, M.B.A., Mark D. McKee, M.D., Andrew Schiermeier, Ph.D., Olivier Harari, M.B., B.Chir., Ph.D., Andrew Murphy, Ph.D., Christos A. Kyratsous, Ph.D., Brian Zambrowicz, Ph.D., Randy Soltys, Ph.D., David E. Gutstein, M.D., John Leonard, M.D., Laura Sepp-Lorenzino, Ph.D., and David Lebwohl, M.D.



Current Pharmaceutical Design, 2023, *29*, 3166-3169

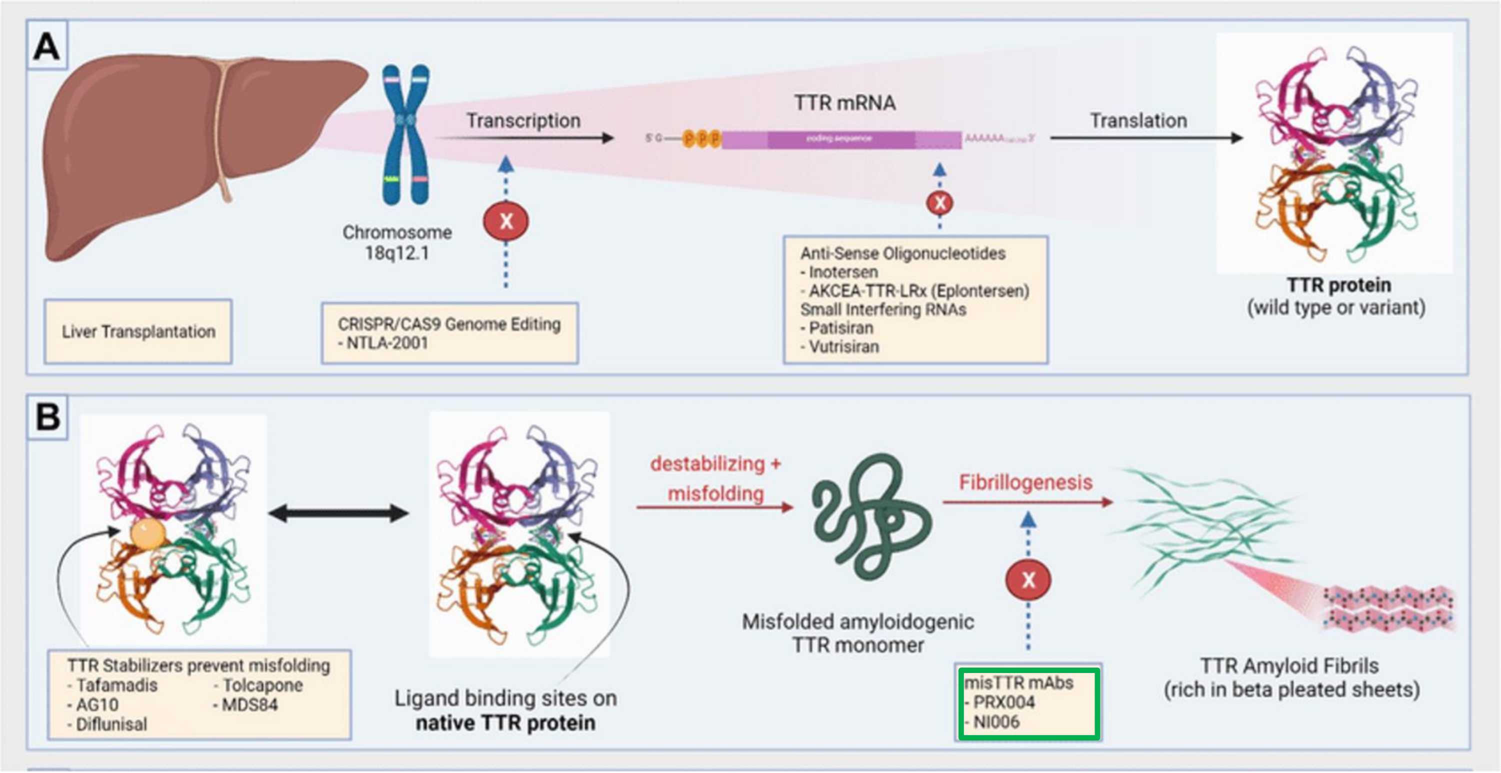
INDUSTRY NEWS

CRISPR-Cas9 for the Treatment of Transthyretin Cardiac Amyloidosis

Lessons from the first-in-human in vivo CRISPR/Cas9 editing of the TTR gene by NTLA-2001 trial in patients with transthyretin amyloidosis with cardiomyopathy

Susy Kotit

Glob Cardiol Sci Pract. 2023 Jan 30;2023(1):e202304.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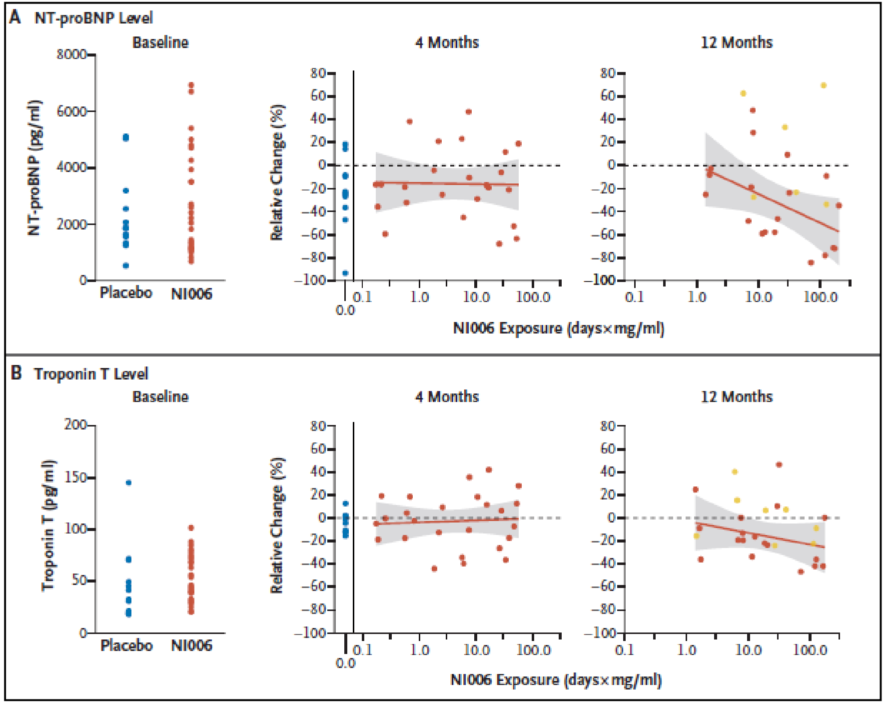
ANTICUERPOS

Phase 1 Trial of Antibody NI006 for Depletion of Cardiac Transthyretin Amyloid

Pablo Garcia-Pavia, M.D., Ph.D., Fabian aus dem Siepen, M.D., Erwan Donal, M.D., Ph.D., Olivier Lairez, M.D., Peter van der Meer, M.D., Ph.D., Arnt V. Kristen, M.D., Michele F. Mercuri, M.D., Ph.D., Aubin Michalon, Ph.D., Robert J.A. Frost, M.D., Ph.D., Jan Grimm, Ph.D., Roger M. Nitsch, M.D., Christoph Hock, M.D., Peter C. Kahr, M.D., and Thibaud Damy, M.D., Ph.D.



Mañana

CRISPR

ATTRv - Polineuropatía

Estadío I

TAFAMIDIS
20 mg oral
diario

Si se objetiva progresión

Vutrisiran o Eplontersen

Estadío II

Vutrisiran o Eplontersen

Anticuerpos

El trasplante hepático se reservará para los pacientes refractarios a los tratamientos propuestos o por decisión unilateral por su parte.

Mañana

ATTR-cardiomiopatía

Tafamidis 61mg oral diario

CRISPR

Acoramidis

Anticuerpos

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Vutrisiran

Eplontersen

MUCHAS GRACIAS

jgonzalez4@hsll.es

ATTR HUSLL

Institut d'Investigació Sanitària Illes Balears
IdISBa

SON LLÀTZER
HOSPITAL UNIVERSITARI