ciberehd
Centro de Investigación Biomédica en Red
Enfermedades Hepáticas y Digestivas

IBiS
INSTITUTODEBIOMEDICINADESEVILLA

Hospital U Virgen del Rocío
UGC Aparato Digestivo

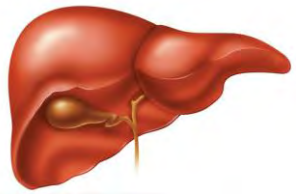
UNIVERSIDAD DE SEVILLA

20 JORNADAS DE AVANCES EN Hepatología

Aula Magna
(Facultad de Medicina)
MÁLAGA

20-21 de Mayo 2021

Enfermedad de Wilson
¿Hay un nuevo horizonte terapéutico?



Dr. Javier Ampuero
UGC Enfermedades Digestivas
Hospital Universitario Virgen del Rocío
Sevilla, España

Enfermedad de Wilson

BRAIN [MARCH, 1912.]

PART IV., VOL. 34.

Original Articles and Clinical Cases.

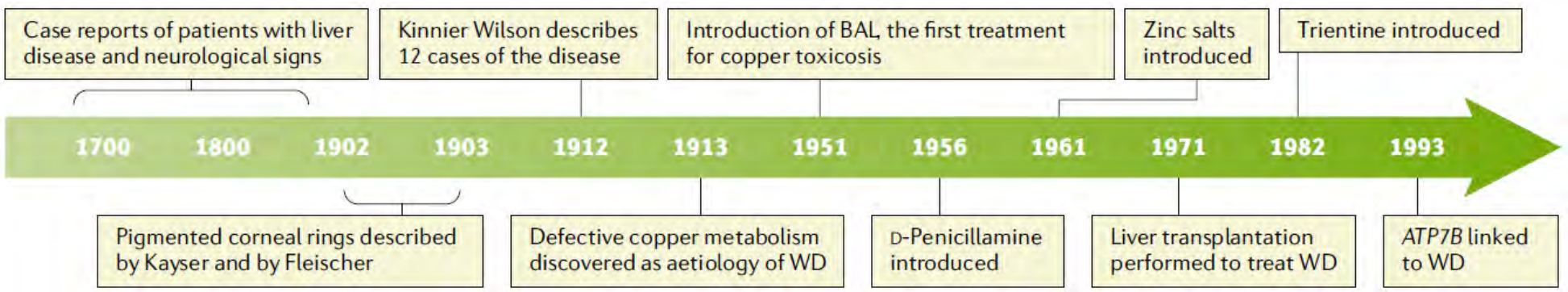
PROGRESSIVE LENTICULAR DEGENERATION: A FAMILIAL NERVOUS DISEASE ASSOCIATED WITH CIRRHOSIS OF THE LIVER.[1]

BY S. A. KINNIER WILSON, M.D., B.Sc.EDIN., M.R.C.P.LOND.

Registrar to the National Hospital, Queen Square, London.

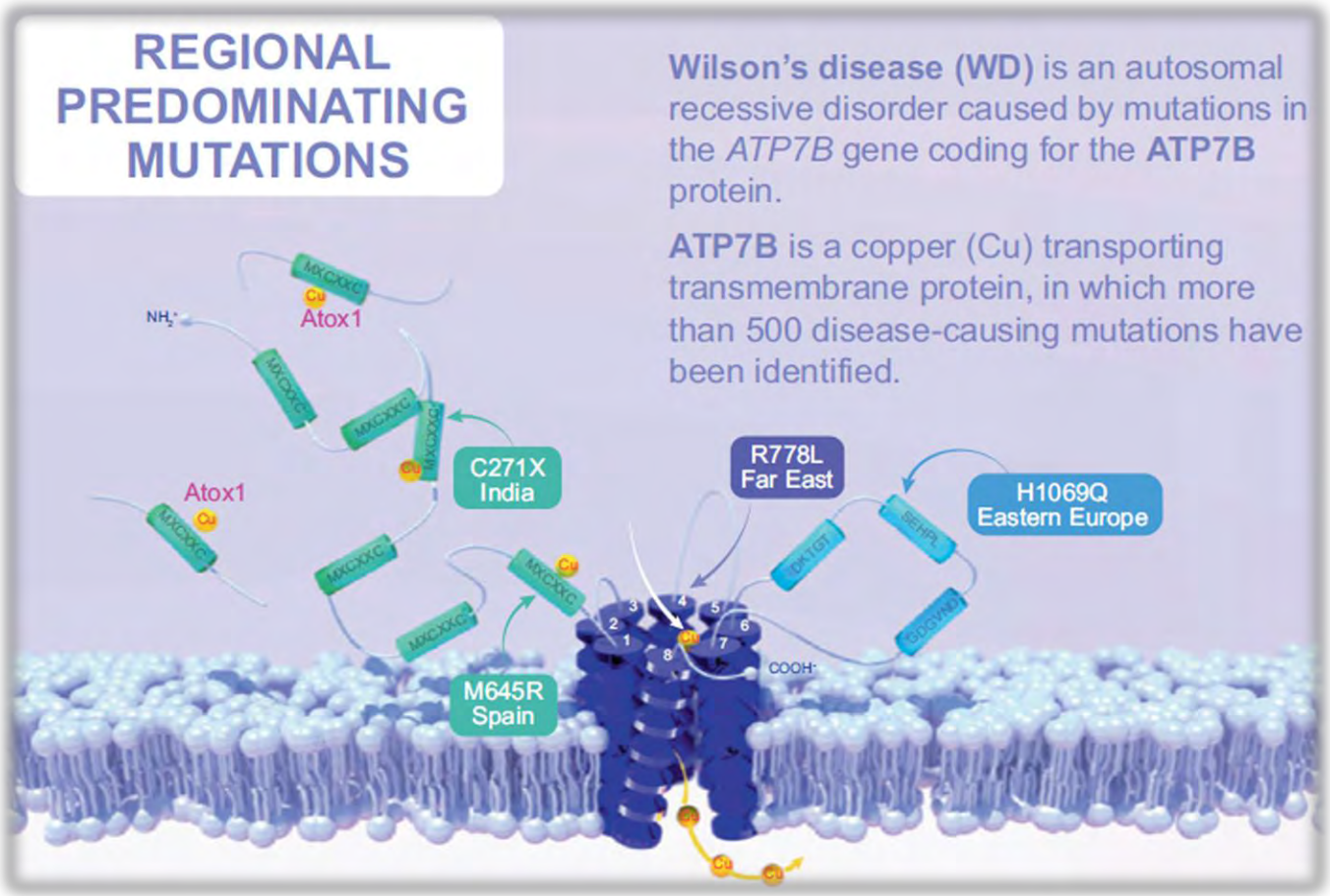
(From the Laboratory of the National Hospital, Queen Square.)

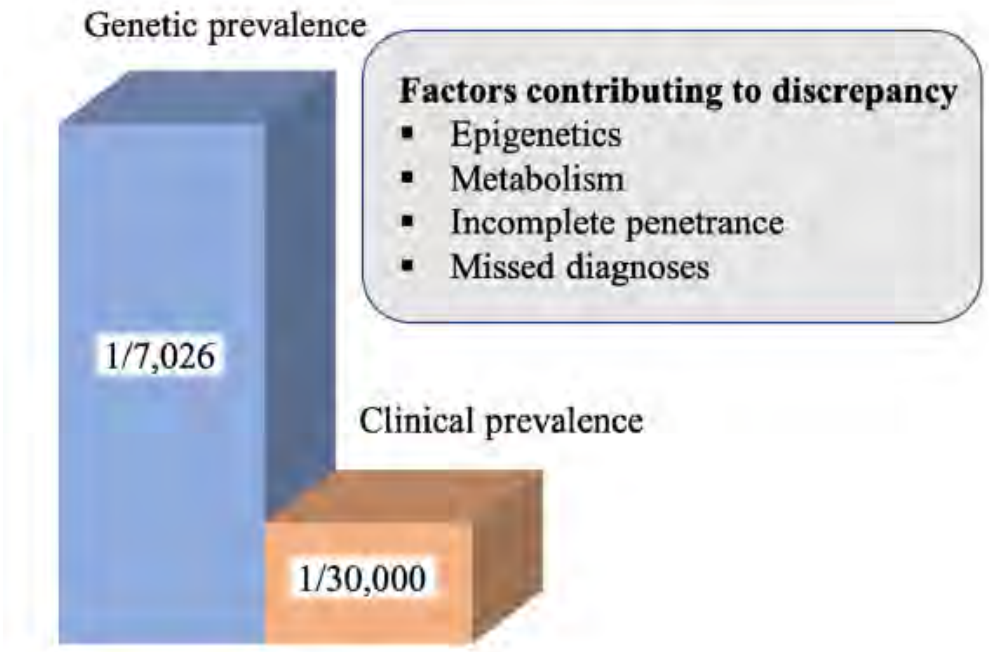
Samuel Alexander Kinnier Wilson (1878–1937)



Członkowska et al. Nat Rev Dis Primers 2018

Broussolle et al. Rev Neurol (Paris) 2013

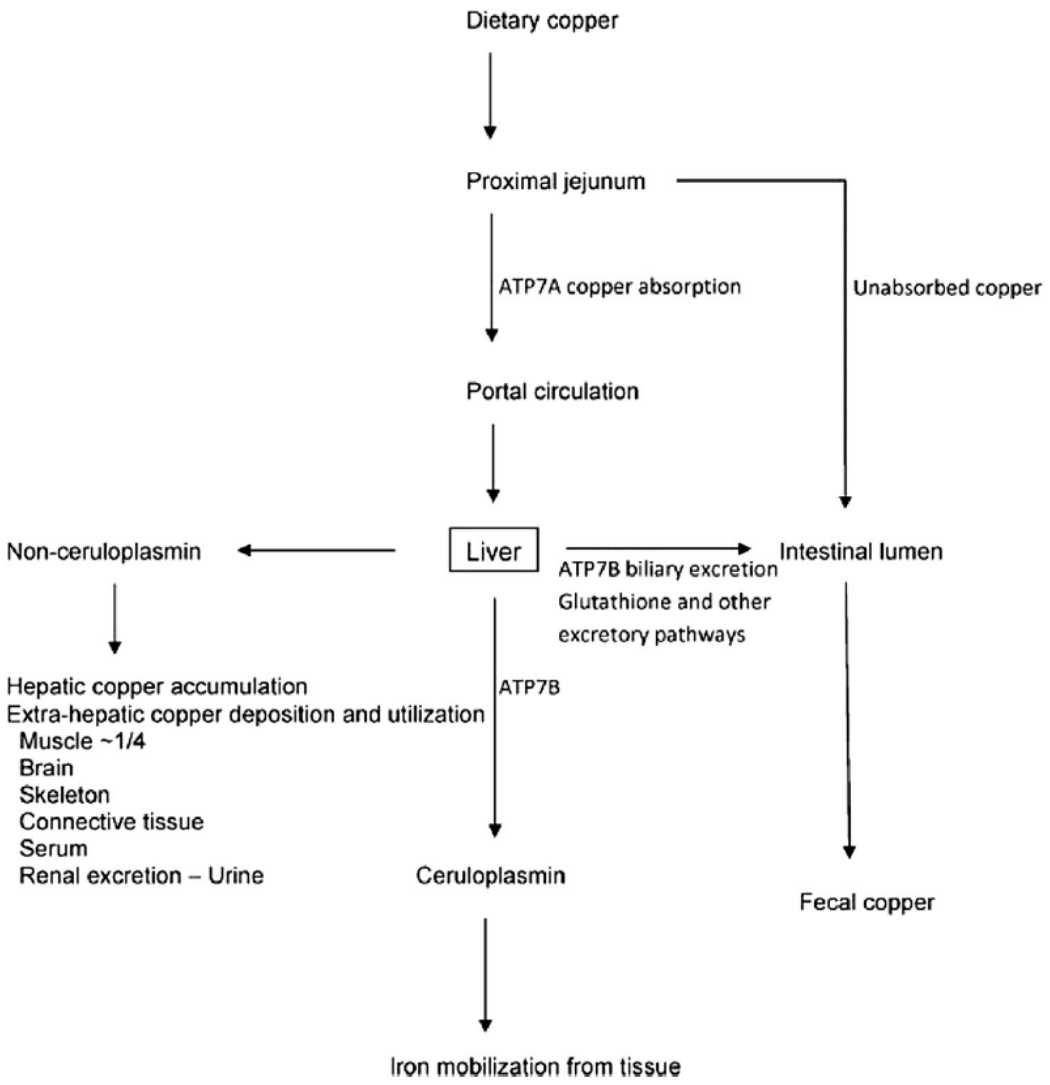


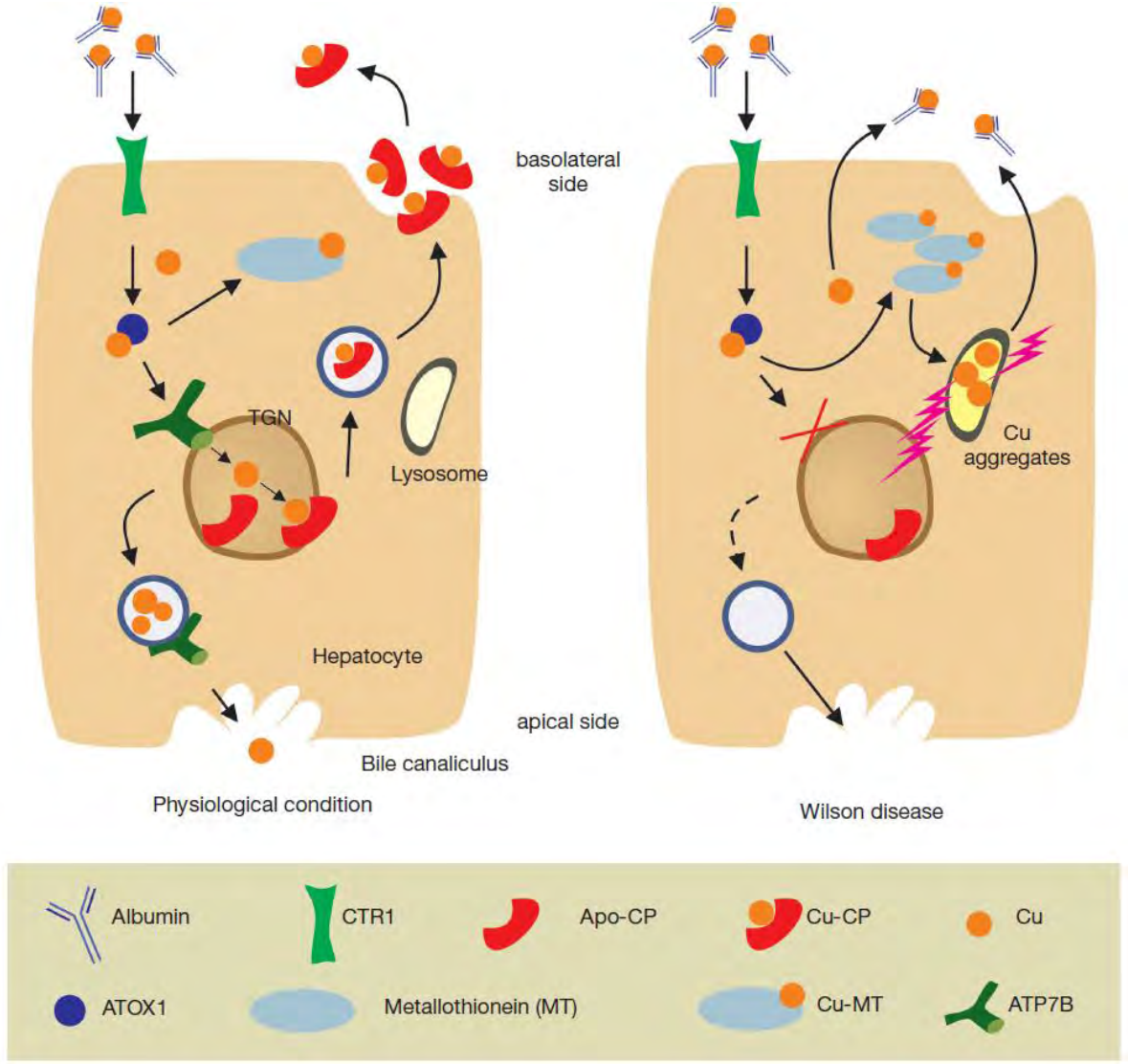


Ferenci et al. J Hepatol 2019

Leung et al. Clin Liver Dis 2021

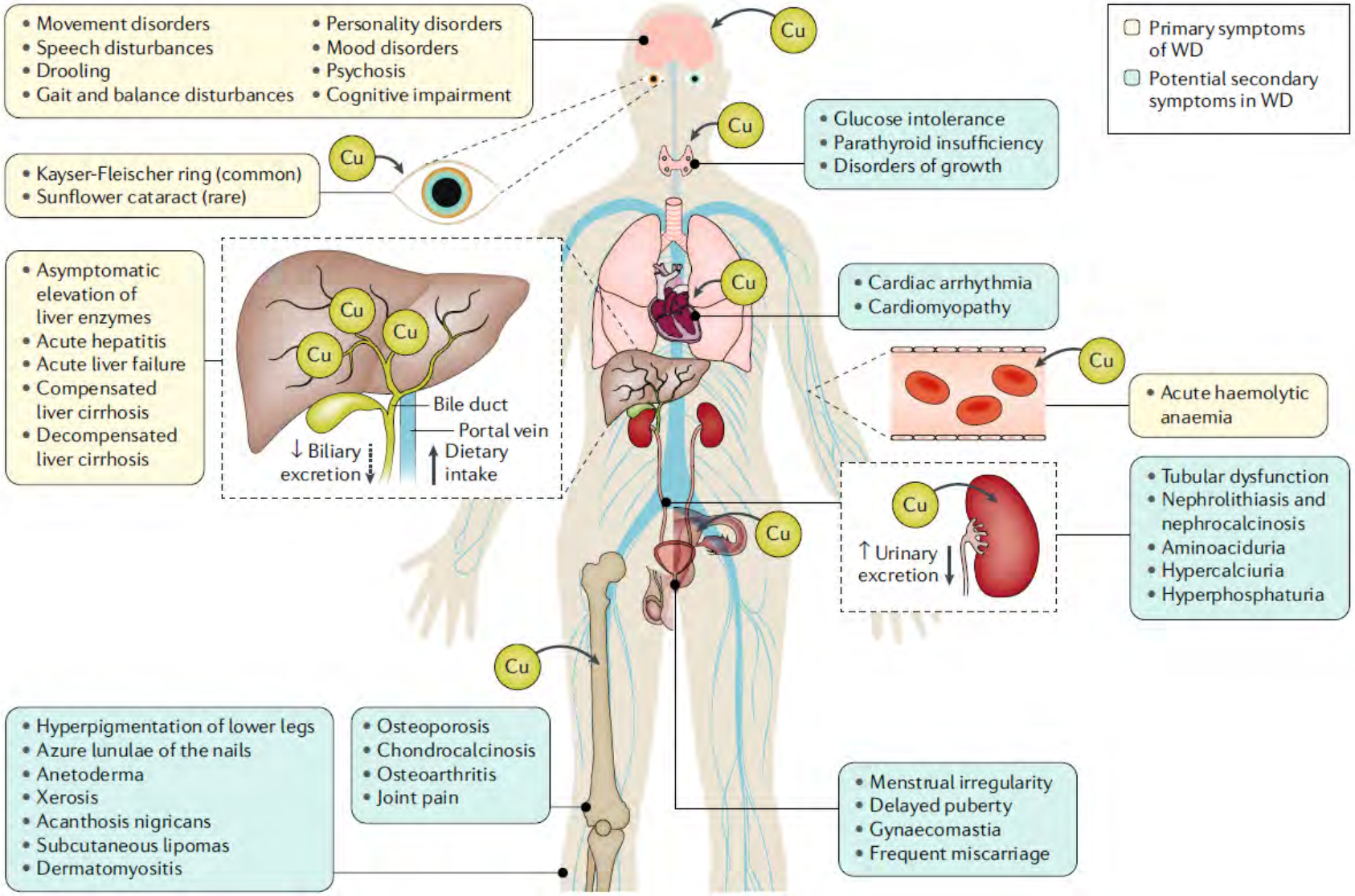
PATOGENIA





Rosencrantz et al. Semin Liver Dis 2011

Stremmel et al. Ann Transl Med 2021



Członkowska et al. Nat Rev Dis Primers 2018

Síntomas y signos clínicos típicos	
Anillos de Kayser-Fleischer	
Presentes	2
Ausentes	0
Síntomas neurológicos**	
Severos	2
Moderados	1
Ausentes	0
Ceruloplasmina sérica	
Normal (>0,2g/L)	0
0,1-0,2g/L	1
<0,1g/L	2
Anemia hemolítica Coombs-negativa	
Presente	1
Ausente	0

Otros tests	
Cobre hepático (en ausencia de colestasis)	
>5x LSN (>4µmol/g)	2
0,8-4µmol/g	1
Normal (<0,8µmol/g)	-1
Gránulos Rodanina-positivos*	1
Cobre urinario (en ausencia de hepatitis aguda)	
Normal	0
1-2xLSN	1
>2xLSN	2
Normal, pero >5xLSN después de la D-penicilmamina	2
Análisis de mutaciones	
Detectadas en ambos cromosomas	4
Detectadas en 1 cromosoma	1
Sin mutaciones detectadas	0

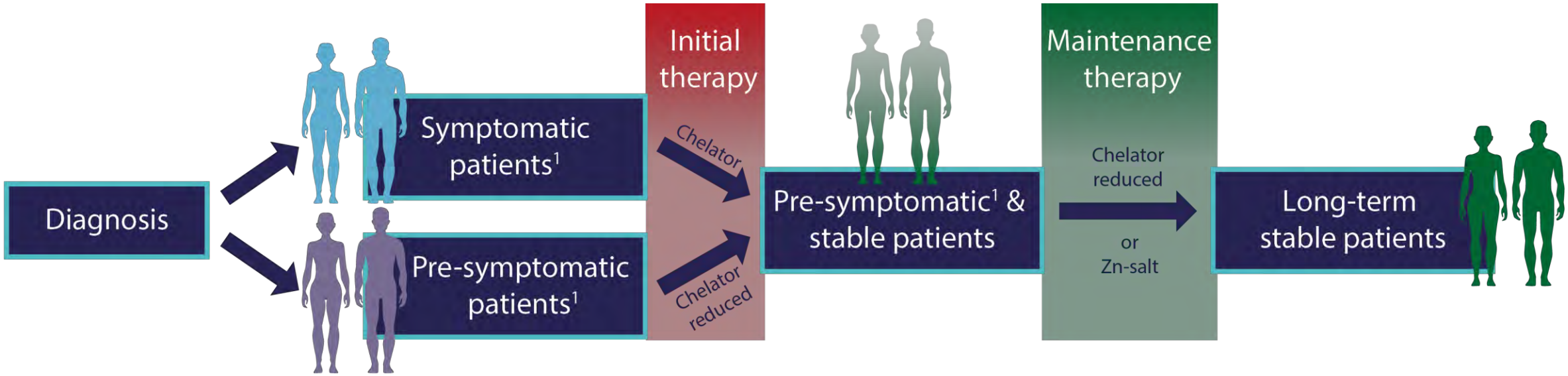
PUNTUACIÓN TOTAL	Resultado evaluación:
4 o más	Diagnóstico confirmado
3	Diagnóstico posible, se necesitan más tests
2 o menos	Diagnóstico poco probable

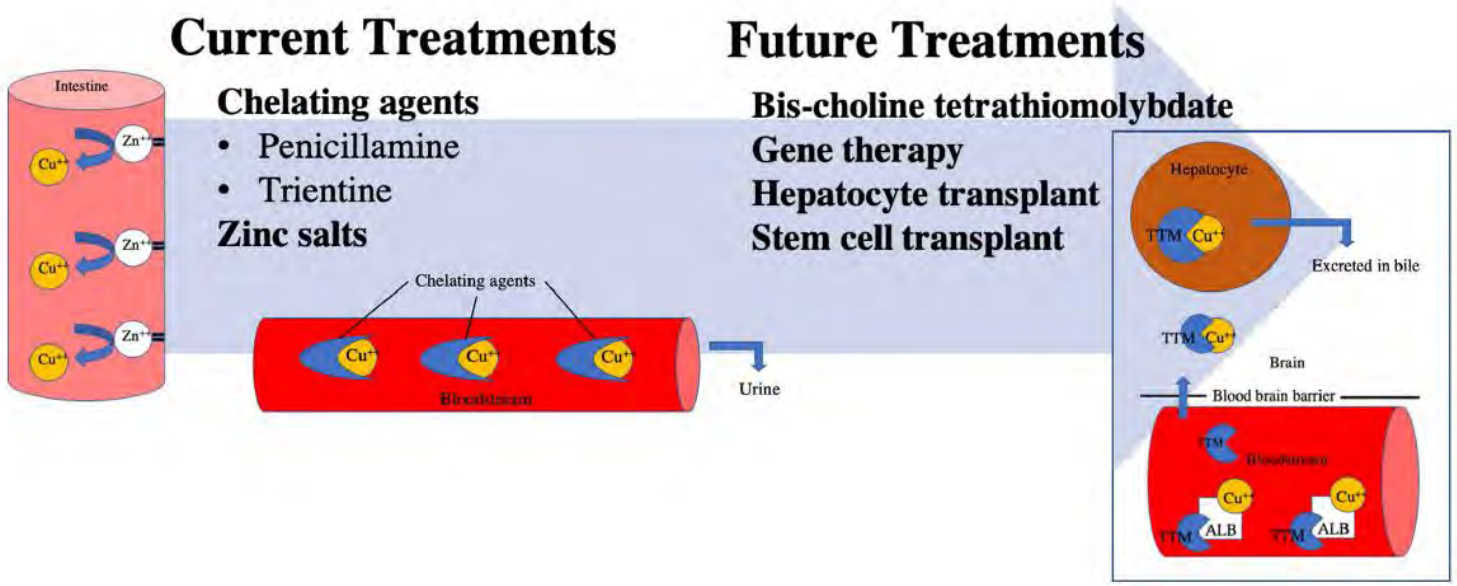
TABLE 2. NEW DIAGNOSTIC TOOLS

Parameter	Description	WD Diagnosis
Radioactive copper (^{64}Cu) ratio	^{64}Cu infused intravenously and measured within the liver and serum after 2, 24, and 48 hours[14]	
24 hours/2 hours		<0.3
48 hours/2 hours		<0.395[14]
Genetic analysis	Polymerase chain reaction amplification of *ATP7B* mutations	Disease-causing mutations
	Whole-genome sequencing: assesses all liver disease genes, not just WD	
REC	Serum assay. REC = exchangeable copper/serum copper	>2.08 µmol/L for extrahepatic disease >1.53 µmol/L for hepatic disease Normal range: 0.62 and 1.15 µmol/L[15]

EASL Guidelines 2012

Leung et al. Clin Liver Dis 2021





Leung et al. Clin Liver Dis 2021

TRATAMIENTO HABITUAL

Medication	Mechanism of action	Side effects	Monitoring	Dose	Other notes
Penicillamine	Copper chelator from hepatic and other stores, induces urinary excretion of copper.	**Early**: fever, cutaneous eruptions, myelosuppression **Late**: nephrotoxicity including nephrotic syndrome, pemphigus or pemphigoid lesions, systemic lupus erythematosus, Goodpasture's syndrome, deleterious effects on vascular collagen.	**Adequacy of treatment**: 24-h urinary copper excretion, 12–32 μmol/day (750–2000 μg/day) after an initial peak. Values below 3.2 μmol/day (200 μg/day), together with serum free copper of >2.36 μmol/l (>150 μg/l) may suggest noncompliance. Serum free copper of <0.79 μmol/l (<50 μg/l) may suggest overtreatment. **For toxicity**: full blood count with liver and renal biochemistry, and urinalysis before initiation and then every 1–2 weeks for the first 2 months, then every 4 weeks.	**Initial**: 125–250 mg/day, increased by 250 mg increments every 4–7 days, to a maximum of 1000–1500 mg/day in 2–4 divided doses **Maintenance**: 750–1000 mg/day, in 2–3 divided doses **Children**: 20 mg/kg/day, in 2–3 divided doses.	Risk of neurological worsening in 10–20% of patients with a neurological presentation when used as initial therapy. Supplemental pyridoxine recommended (25–50 mg/day).
Trientine	Copper chelator, induces urinary excretion of copper.	Similar to penicillamine but at a much lower frequency. Most common is proteinuria.	**Adequacy of treatment**: similar to penicillamine. **For toxicity**: No laboratory studies necessary but good practice to monitor counts and urinalysis as for penicillamine.	**Initial**: 750–1500 mg/day, in 2–3 divided doses. **Maintenance**: 750–1000 mg/day, in 2–3 divided doses. **Children**: 20 mg/kg/day, in 2–3 divided doses.	Risk of neurological worsening after initiating therapy is <20% and lower than the risk from penicillamine.
Zinc	Induces metallothionein and inhibits absorption of copper with faecal excretion.	Gastric irritation. Has an otherwise excellent safety profile.	**Adequacy of treatment**: 24-h urinary copper excretion (usually <1.2 μmol/day while on maintenance therapy). Urinary zinc levels and serum free copper may also be measured. **For toxicity**: No laboratory studies are necessary.	**Initial**: controversial and not currently recommended for initial monotherapy. **Maintenance**: 150 mg/day of elemental zinc for larger adults and children (75 mg/day if less than 50 kg), in three divided doses.	Asymptomatic patients may be treated with maintenance dosages of zinc monotherapy.

Kathawala et al. Ther Adv Gastroenterol 2017

ESQUEMA DE TRATAMIENTO: QUELANTES Y ZINC

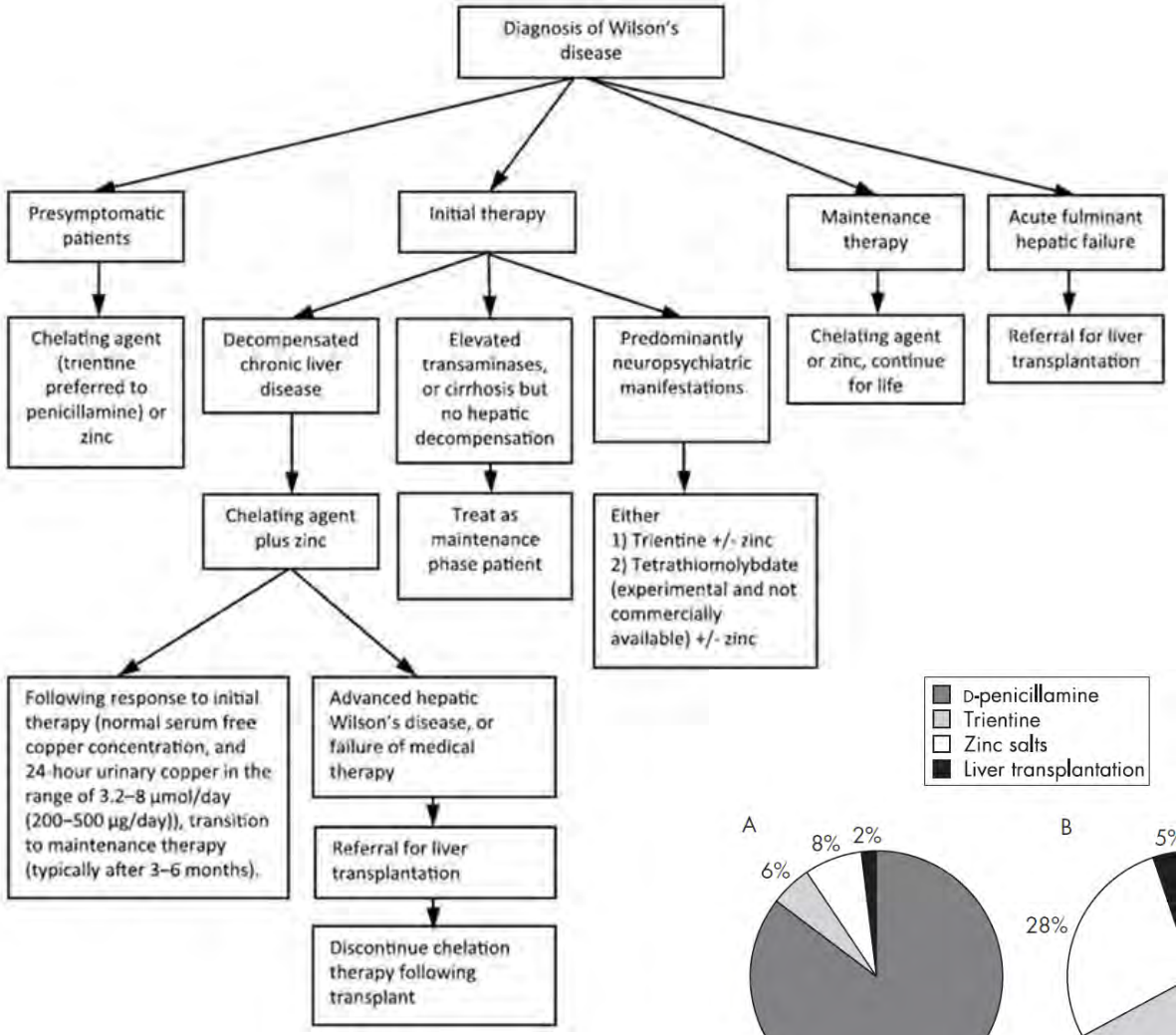
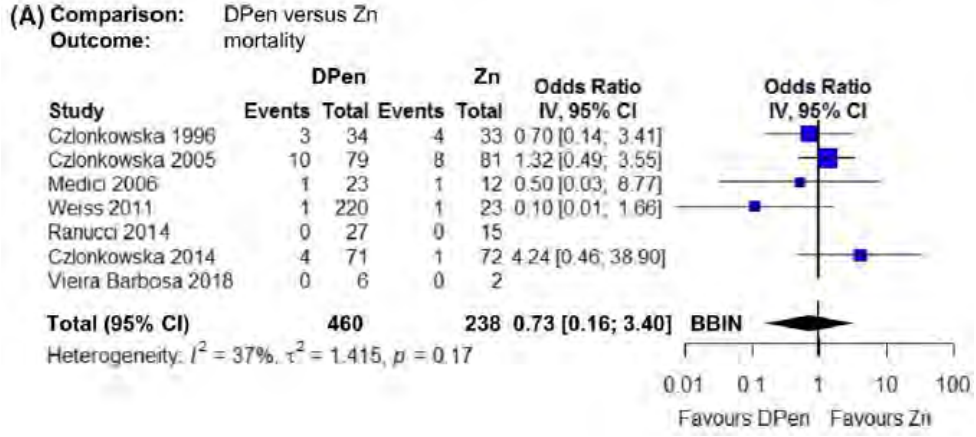
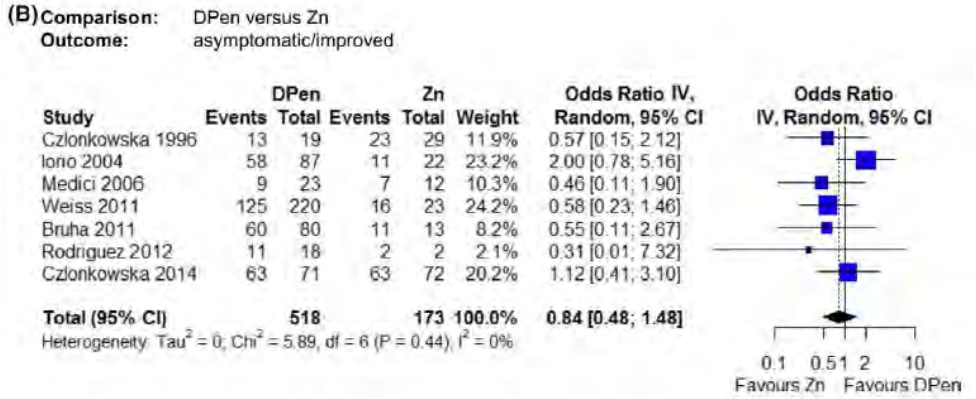


Figure 2 Treatment of patients with Wilson's disease (A) at diagnosis and (B) at the end of the study.





Merle et al. Gut 2007

Kathawala et al. Ther Adv Gastroenterol 2017

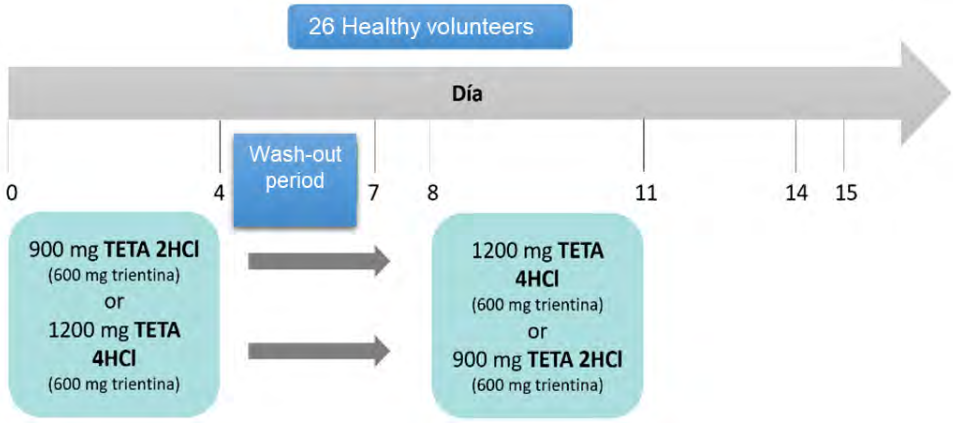
Appenzeller-Herzog et al. Liver Int 2019

Table 3. Details of Patients Who Failed to Respond to Treatment

						Event "treatment failure" occurred				
Patient no.	Sex	Diagnosis by family screening	Initial presentation	Kayser-Fleischer rings at diagnosis	Liver cirrhosis at diagnosis	Under therapy with	Time on this medication (*y*)	Time from diagnosis to failure (*y*)	First-line therapy	Rescue therapy
7	Female	No	Hepatic	None	None	Zinc	9.93	17.05	D-penicillamine	Trientine
15	Male	No	Hepatic	Yes	Yes	Zinc	1.16	34.75	D-penicillamine	Trientine
25	Female	No	Asymptomatic	Yes	None	Zinc	3.63	7.99	D-penicillamine	Trieninte
31	Female	Yes	Hepatic	Not determined	None	Zinc	1.00	13.01	D-penicillamine	D-penicillamine
39	Female	Yes	Hepatic	None	Yes	Zinc	3.11	3.11	Zinc	Trientine
69	Male	No	Mixed	Yes	Yes	Zinc	1.18	27.26	D-penicillamine	D-penicillamine
72	Female	No	Neurological	Yes	None	Zinc	18.34	34.35	D-penicillamine	Trientine
88	Female	Yes	Asymptomatic	None	None	Trientine	1.45	14.06	D-penicillamine	Zinc (in follow-up: zinc failure; final successful rescue treatment: D-penicillamine)
88	Female	Yes	Asymptomatic	None	None	Zinc	3.94	18.00	D-penicillamine	D-penicillamine
91	Male	Yes	Hepatic	None	None	Zinc	2.70	6.65	D-penicillamine	D-penicillamine
94	Female	No	Hepatic	None	None	Zinc	3.50	3.75	D-penicillamine	Combination
94	Female	No	Hepatic	None	None	Trientine	2.30	14.90	D-penicillamine	D-penicillamine
104	Male	Yes	Hepatic	None	None	Zinc	0.67	0.83	Zinc	D-penicillamine
127	Male	No	Neurologic	None	None	Zinc	1.06	1.96	Zinc	Combination
135	Male	Yes	Hepatic	Yes	None	Zinc	2.52	15.33	D-penicillamine	Trientine
177	Female	No	Neurologic	None	Yes	Trientine	0.50	0.76	Zinc	D-penicillamine
184	Male	No	Hepatic	Yes	Yes	D-penicillamine	26.68	26.68	D-penicillamine	Trientine
205	Male	No	Hepatic	Not determined	Yes	Zinc	8.33	8.50	D-penicillamine	OLT
215	Male	No	Hepatic	None	None	Combination	2.08	2.08	Combination	D-penicillamine

Weiss et al. Gastroenterology 2011

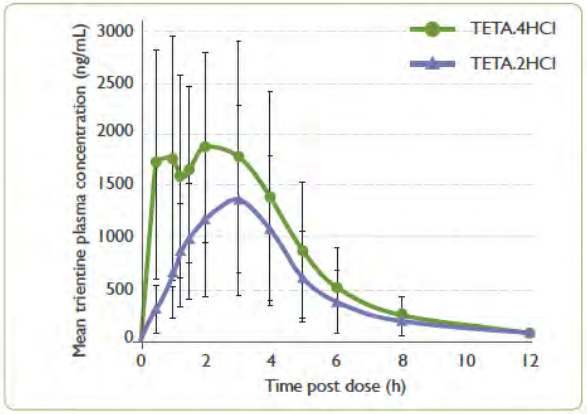
TRIENTINA: TETA 4HCL VS TETA 2HCL



TETA.4HCl showed considerably greater Trientine bioavailability vs. TETA.2HCl.

Mean (SD)	TETA.4HCl	TETA.2HCl
C_{max}	2340 ng/mL (1170)	1490 ng/mL (864)
AUC_{0-t}	10100 ng.hr/mL (5740)	6600 ng.hr/mL (3870)

TRIUMPH-1 STUDY



TRIUMPH-2 STUDY

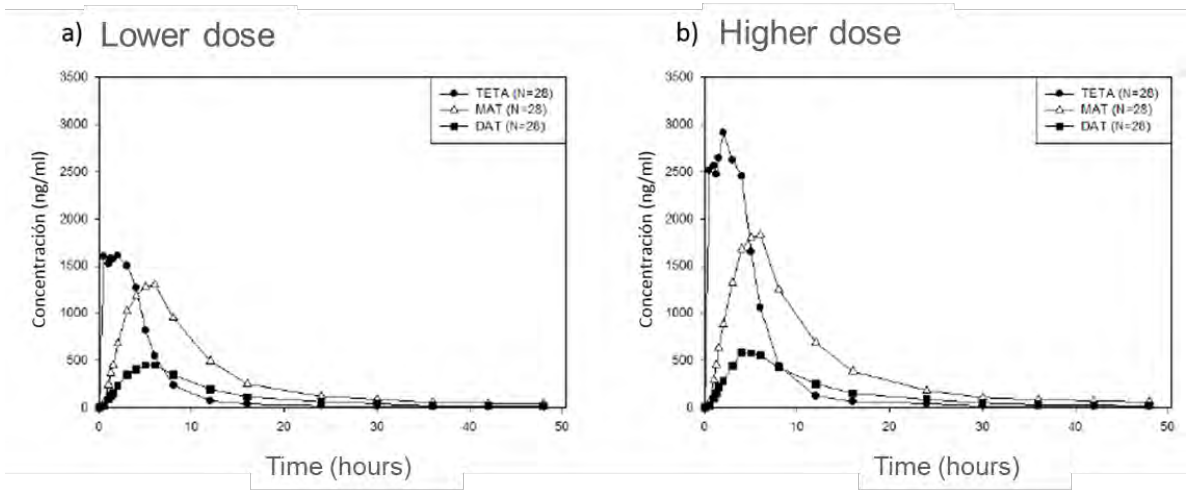
Design:
- Phase I
- Single center
- Randomized
- Interventional
- Open-label
- 4-way crossover study

Eligible patients:
- Healthy adult volunteers (n=28)

Methods

Single oral administration of each of the following in a randomized crossover design:

- TETA 2HCl "lower dose" = 3 capsules (500mg trientine base)
- TETA 2HCl "higher dose" = 5 capsules (833mg trientine base)
- TETA 4HCl "lower dose" = 3 tablets (450mg trientine base)
- TETA 4HCl "higher dose" = 5 tablets (750mg trientine base)



Adjustement factor 0.6 based on Cmax and 0.64 based on the area under the curve (AUC)

Weiss et al. The International Liver Congress. 27th- 29th August 2020. DOI: 10.3252/pso.eu.ILC2020

TRIENTINA: TETA 4HCL VS TETA 2HCL

	Trientine 4HCl	Trientine 2HCl
Handling	Easy to use • Blister package with film-coated tablets • Easy to swallow[1]	Available only as vials[2]
Storage	No particular storage limitations • No cooling required[1]	Cooled storage necessary (2-8° C)[2]
Dosage	Individual Dosage • Dividable film-coated tablets[1]	Cannot be divided (capsules)[2]
Additives	• Gelatine free and lactose free[1]	Contains gelatine[2]
Daily consumption	Low daily consumption • Dosage for adults: 3 to 6 1/2 tablets daily[1]	High daily consumption: • Dosage for adults: 4 to 8 Capsules daily[2]

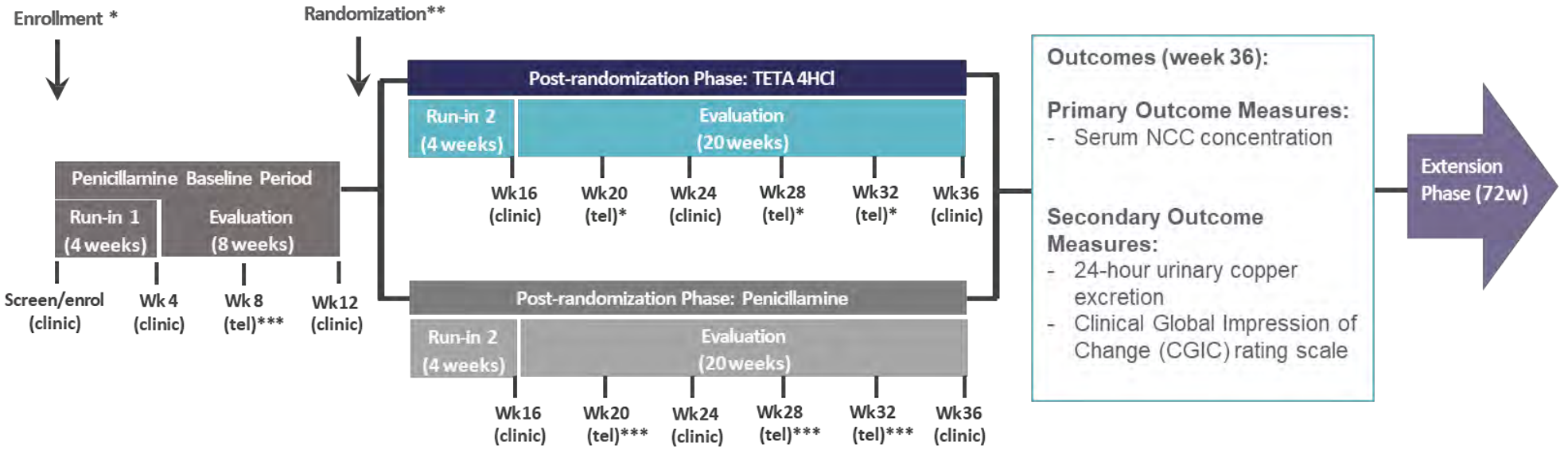
*TETA 4HCl no está comercializado en España
**TETA 2HCl no está comercializado en España

1. Cuprior®. Summary of Product Characteristics, June 2020
2. Cufence®. Summary of Product Characteristics, March 2020

CHELATOR STUDY

Design:
- Multicentre
- Randomized
- Open label study with standard-of-care active comparator

Eligible patients:
- n= 55 WD pat
- 18-75 years old
- Tolerating and well-controlled on DPA per 1 year



Outcomes (week 36):

Primary Outcome Measures:
- Serum NCC concentration

Secondary Outcome Measures:
- 24-hour urinary copper excretion
- Clinical Global Impression of Change (CGIC) rating scale

Extension Phase (72w)

Extension Phase (72 weeks)

Continue allocated TETA 4HCl or penicillamine for further 24 weeks, then all receive TETA 4HCl for 48 weeks

Clinic visits at Wk 60, Wk 84, and Wk 108 for all patients (additional visit at Wk 64 for patients previously in penicillamine arm)

* Enrollment of stable patients receiving penicillamine for ≥ 52 weeks, stable dose for ≥ 16 weeks

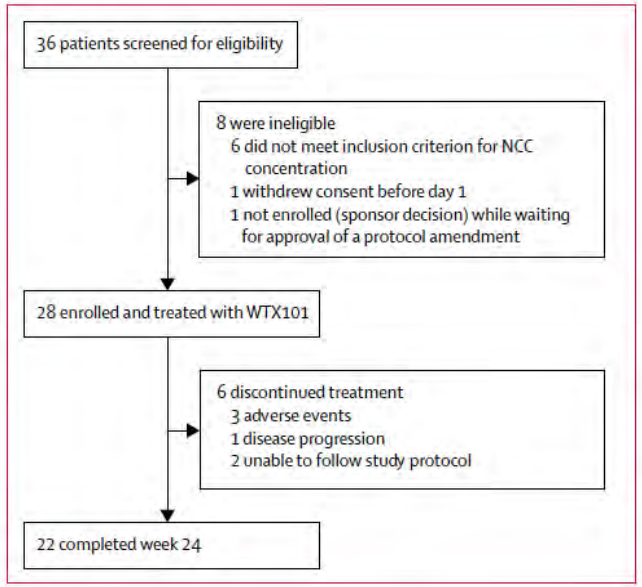
** Randomization of adequately controlled patients per protocol criteria

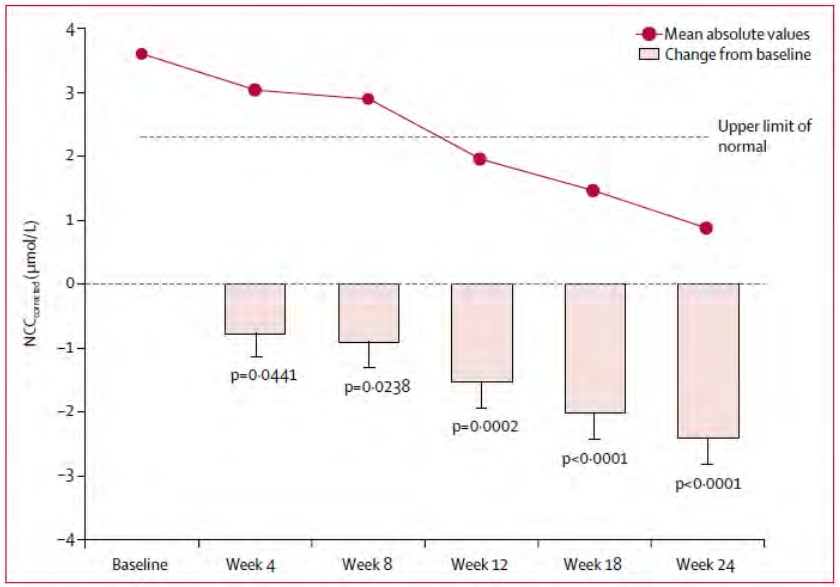
*** May be telephone visit with lab samples obtained directly from patient

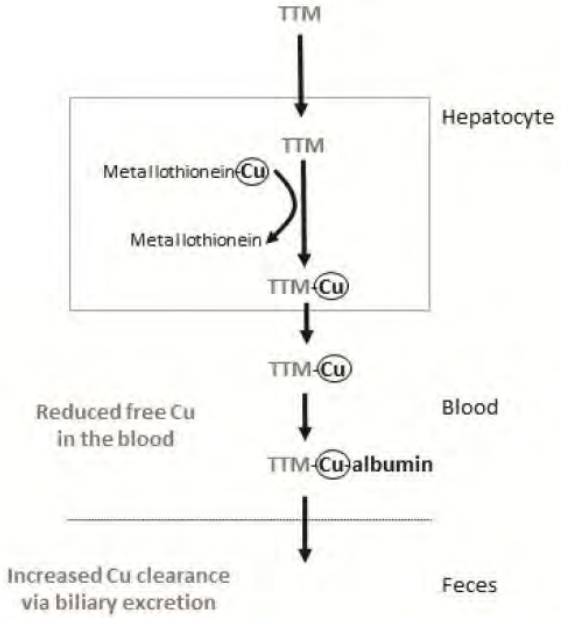
*TETA 4HCl no está comercializado en España

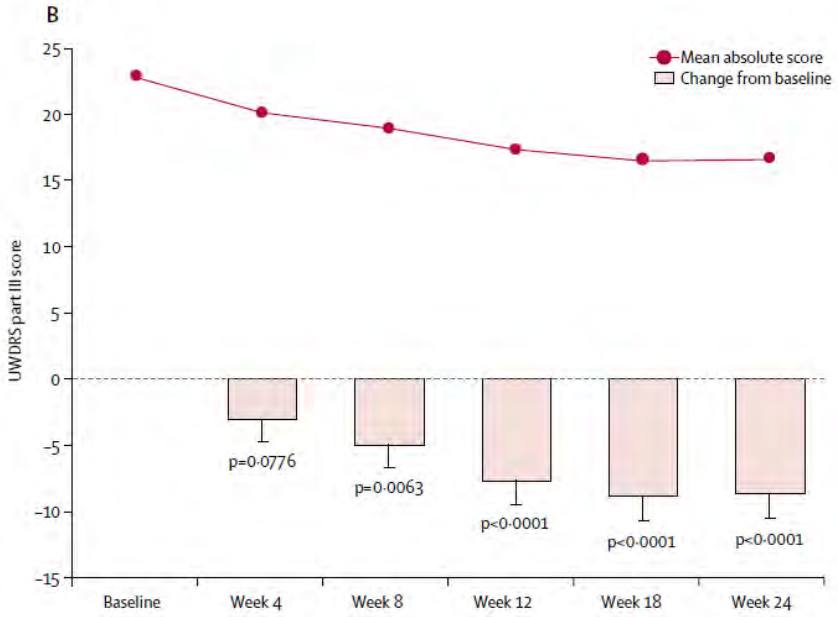
https://clinicaltrials.gov/ct2/show/NCT03539952 accessed December 2020

TETRATIOMOLIBDATO DE BISCOLINA (WTX101)





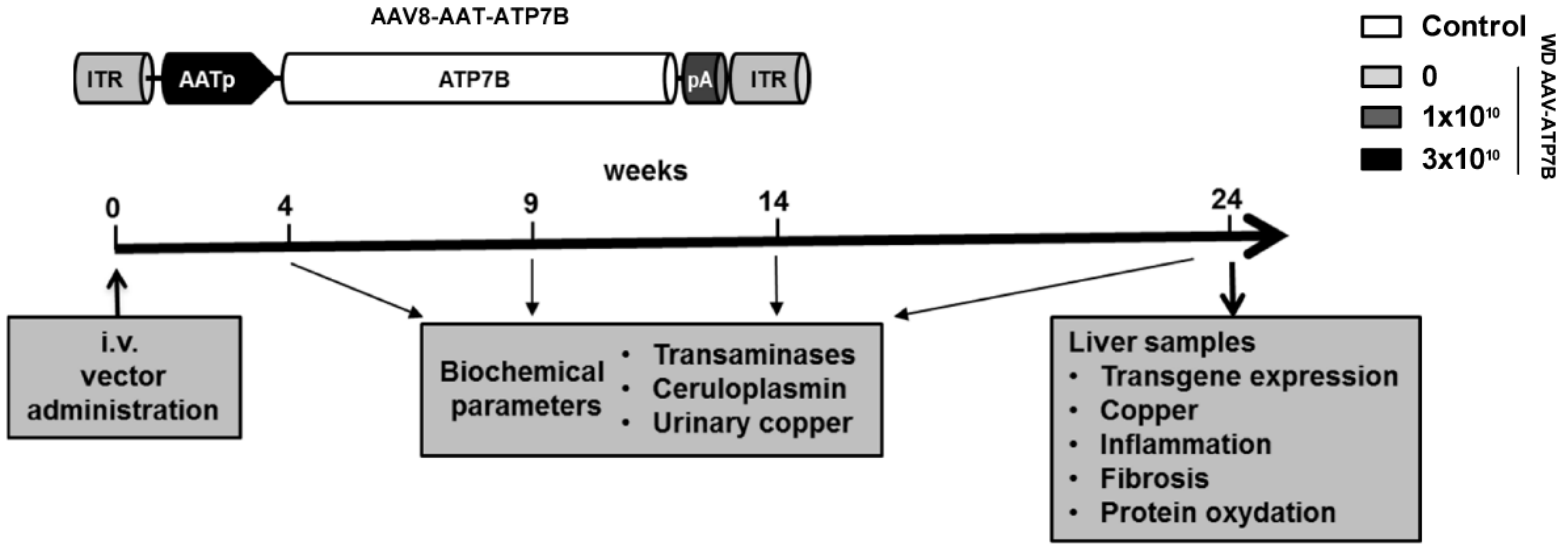


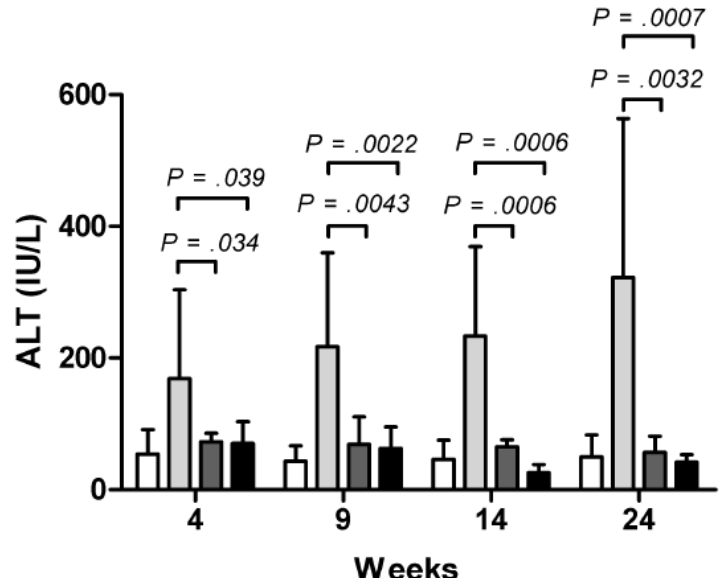


	Number of patients (%)
Patients reporting at least one treatment-emergent adverse event	17 (61%)
ALT increased	8 (29%)
GGT increased	8 (29%)
AST increased	7 (25%)
Hepatic enzyme increased	4 (14%)
Blood alkaline phosphatase increased	3 (11%)
Headache	2 (7%)
Tremor	2 (7%)
Nausea	2 (7%)
Dry skin	2 (7%)
Leukopenia	2 (7%)
Patients reporting at least one treatment-emergent serious adverse event	7 (25%)
Psychotic disorder	1 (4%)
Abnormal behaviour	1 (4%)
Adjustment disorder	1 (4%)
Affective disorder	1 (4%)
Mania	1 (4%)
Personality disorder	1 (4%)
ALT increased	1 (4%)
Hepatic enzyme increased (severe increase in ALT or AST)	1 (4%)
Gait disturbance	1 (4%)
Agranulocytosis	1 (4%)
Decline in neurological functioning	1 (4%)

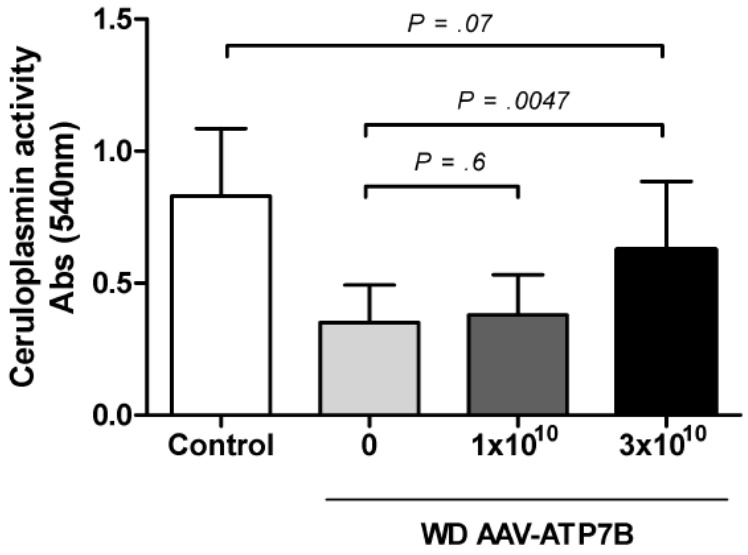
Weiss et al. Lancet GH 2017

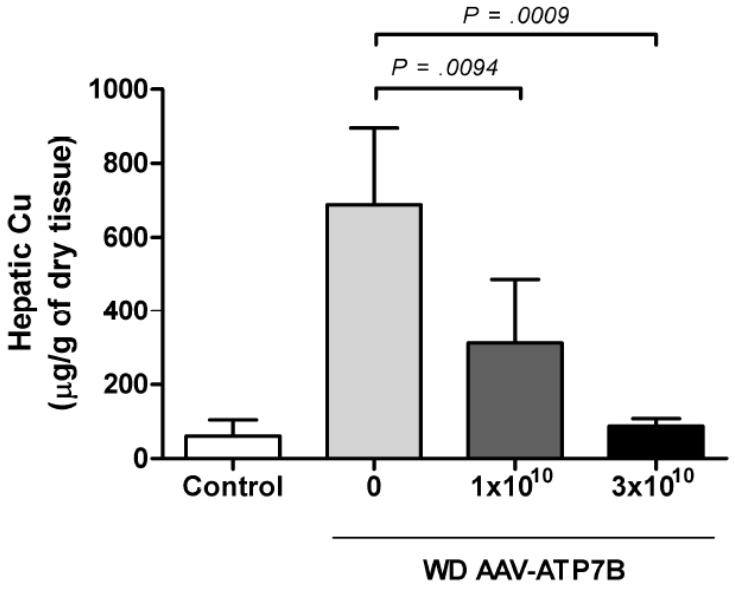
Weiss et al. Expert Opin Investig Drug 2018

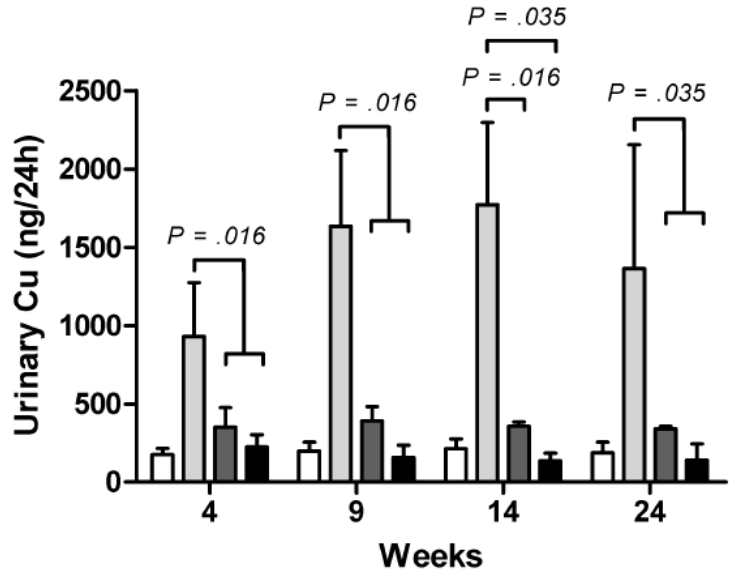




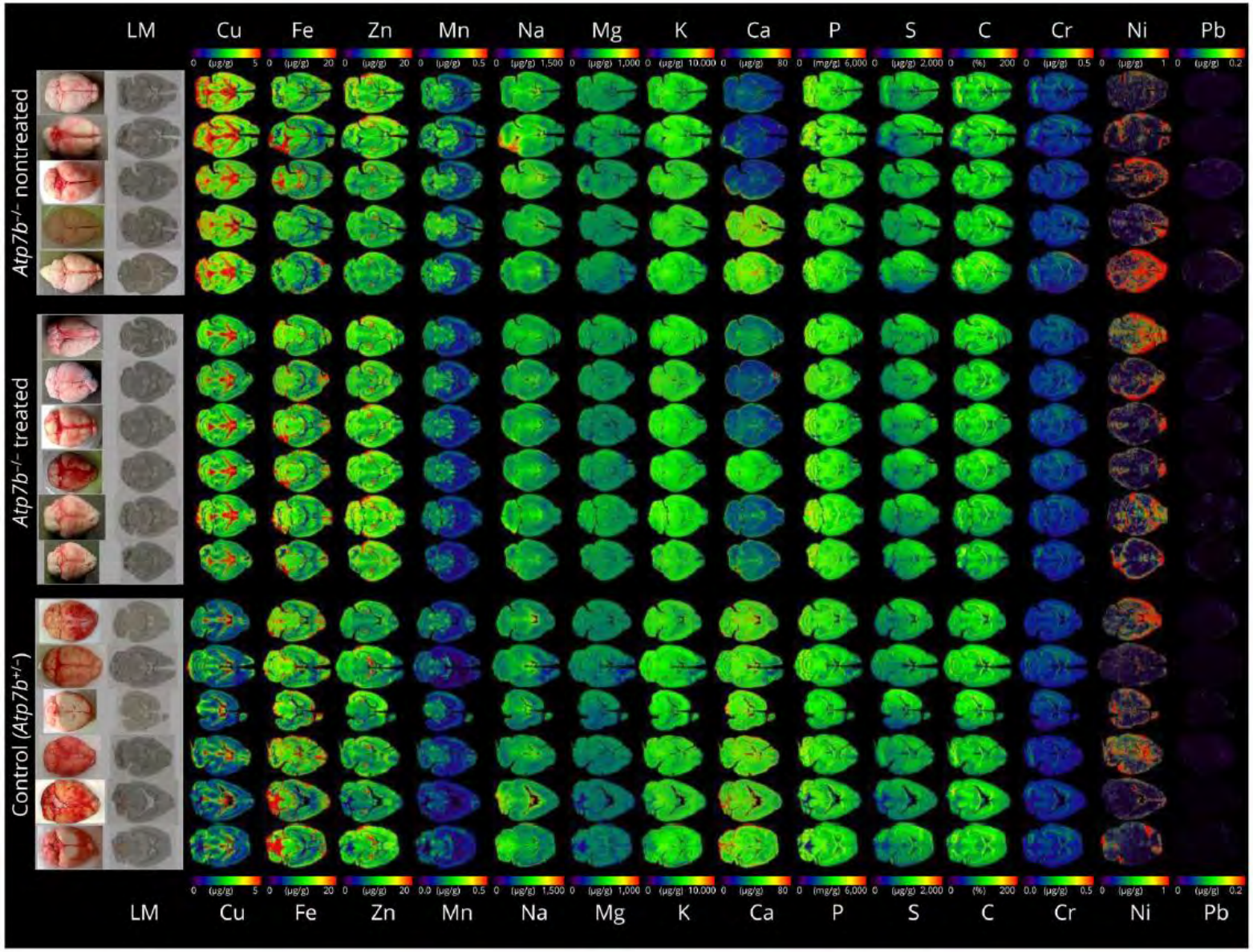
A

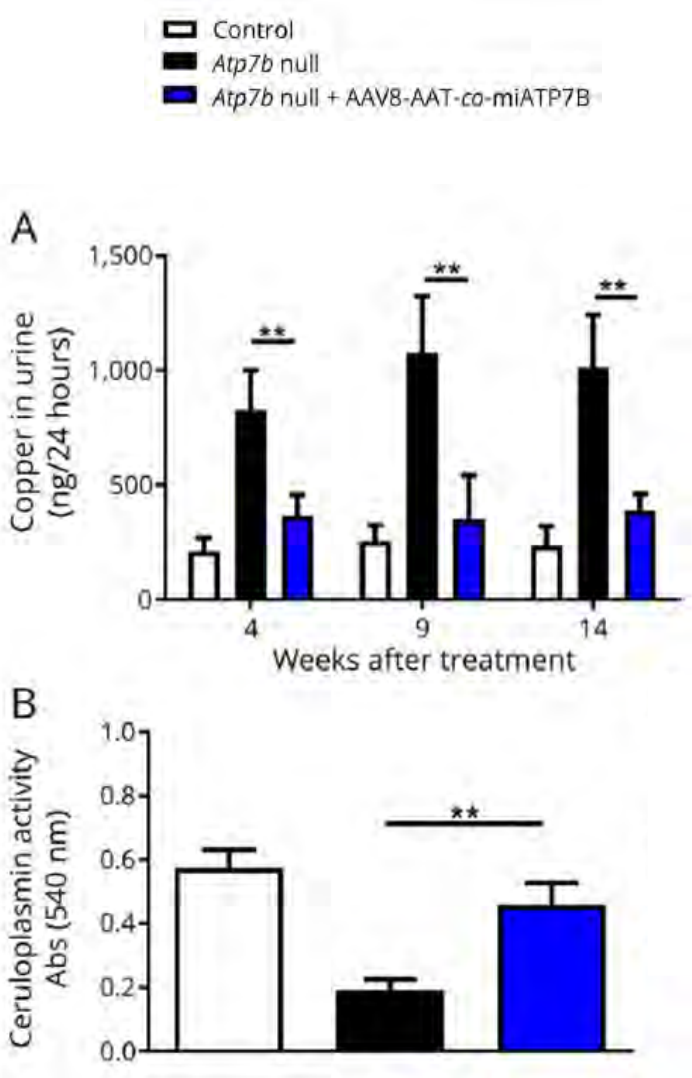






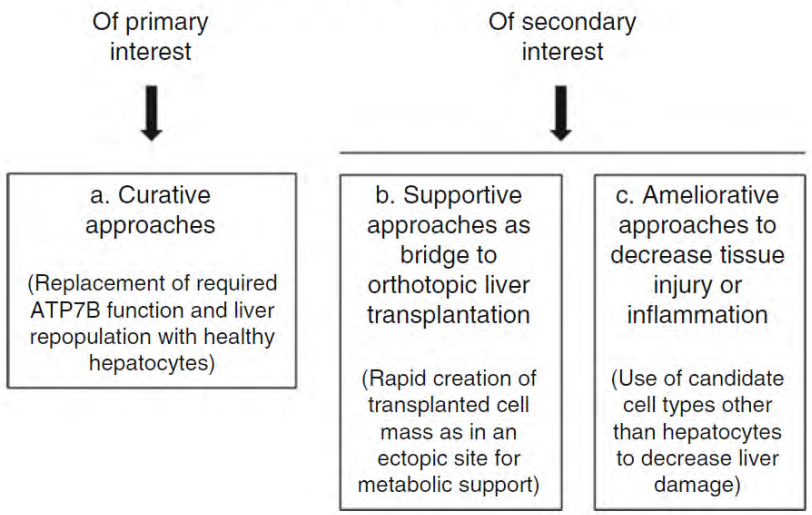
Murillo et al. J Hepatol 2016

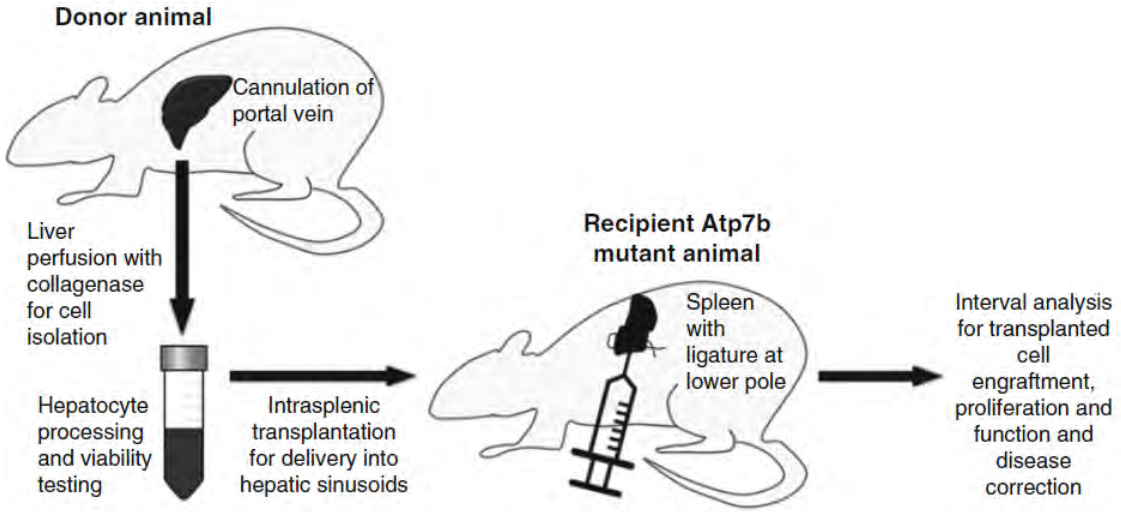




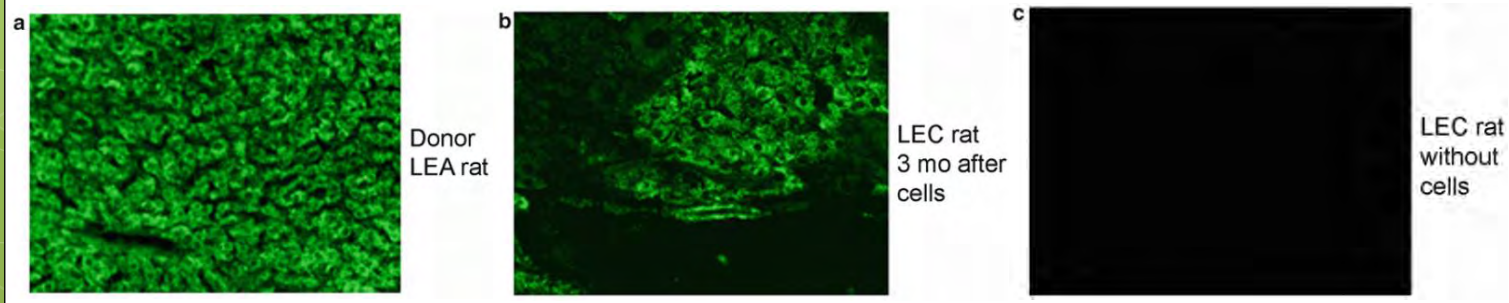
Uerlings et al. Neurol Genet 2018

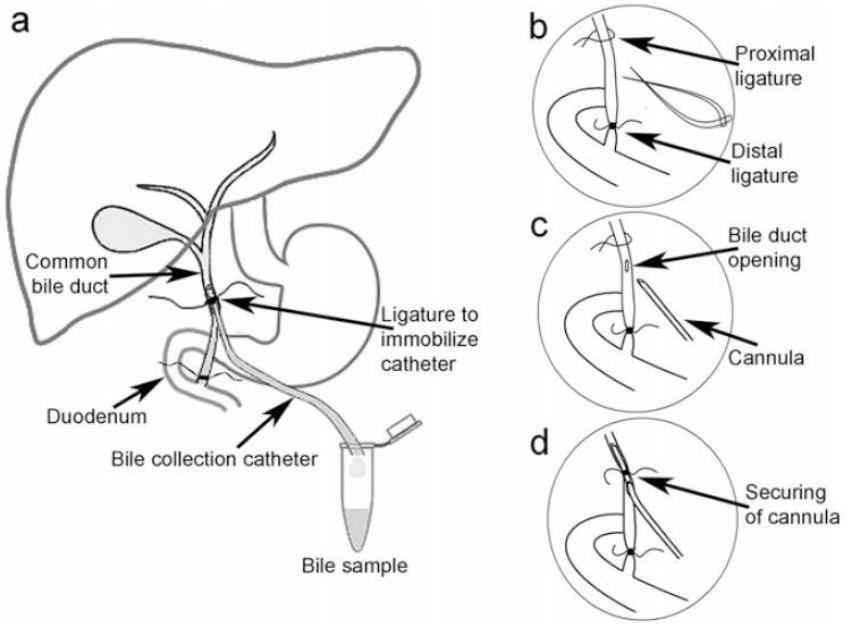
Relevant mechanisms for cell therapy in Wilson's disease





Hepatocytes derived from pluripotent stem cells[a]	Stem cells from adult liver[b]	Hepatocytes derived from extrahepatic stem cells[c]
Embryonic stem cells	Hepatocyte subpopulations	Hematopoietic stem cells from bone marrow, peripheral blood, cord blood, etc.
Fetal liver stem cells	Oval cell populations	Mesenchymal stem cells
Induced pluripotent stem cells	Other cell types	Amniotic or placental stem cells





Jaber et al. Methods Mol Biol 2017

Gupta et al. Ann NY Acad Sci 2014

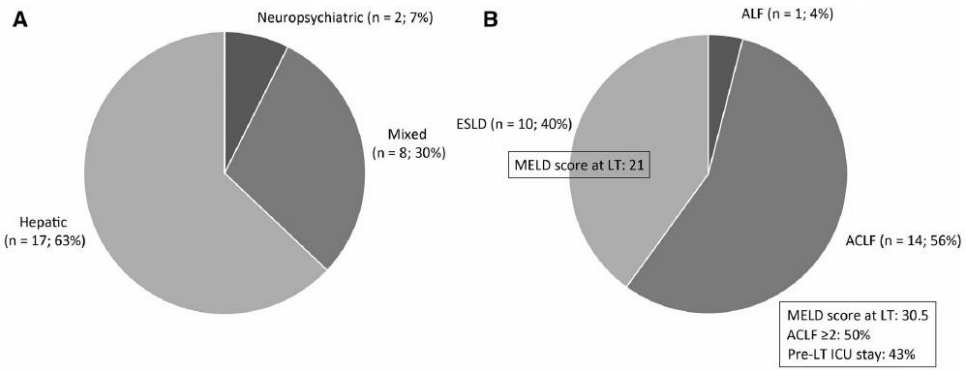
Table 4 | **Wilson disease prognostic index**

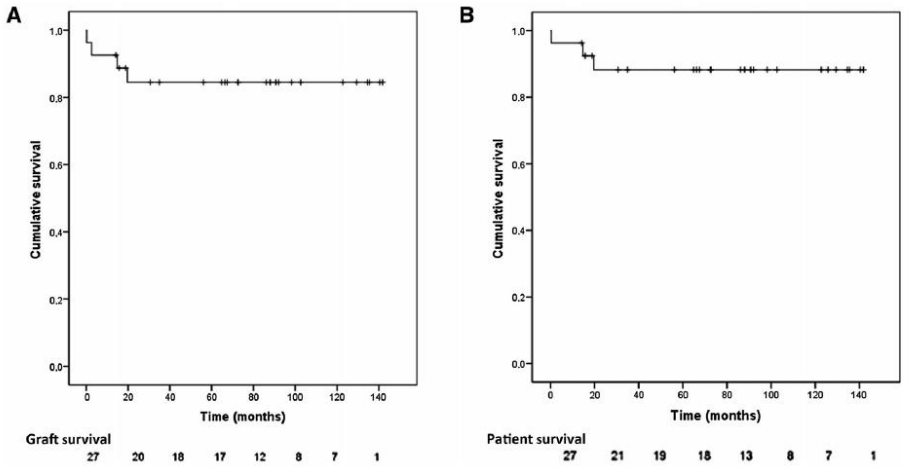
Parameter	0 points	1 point	2 points	3 points	4 points
Serum bilirubin (micromoles per litre)	0–100	101–150	151–200	201–300	>301
Aspartate aminotransferase (units per litre)	0–100	101–150	151–300	301–400	>401
International normalized ratio	0–1.29	1.3–1.6	1.7–1.9	2.0–2.4	>2.5
White blood cell count (10^9 per litre)	0–6.7	6.8–8.3	8.4–10.3	10.4–15.3	>15.4
Albumin (grams per litre)	>45	34–44	25–33	21–24	<20

A score of ≥ 11 points is associated with high probability of death without liver transplantation

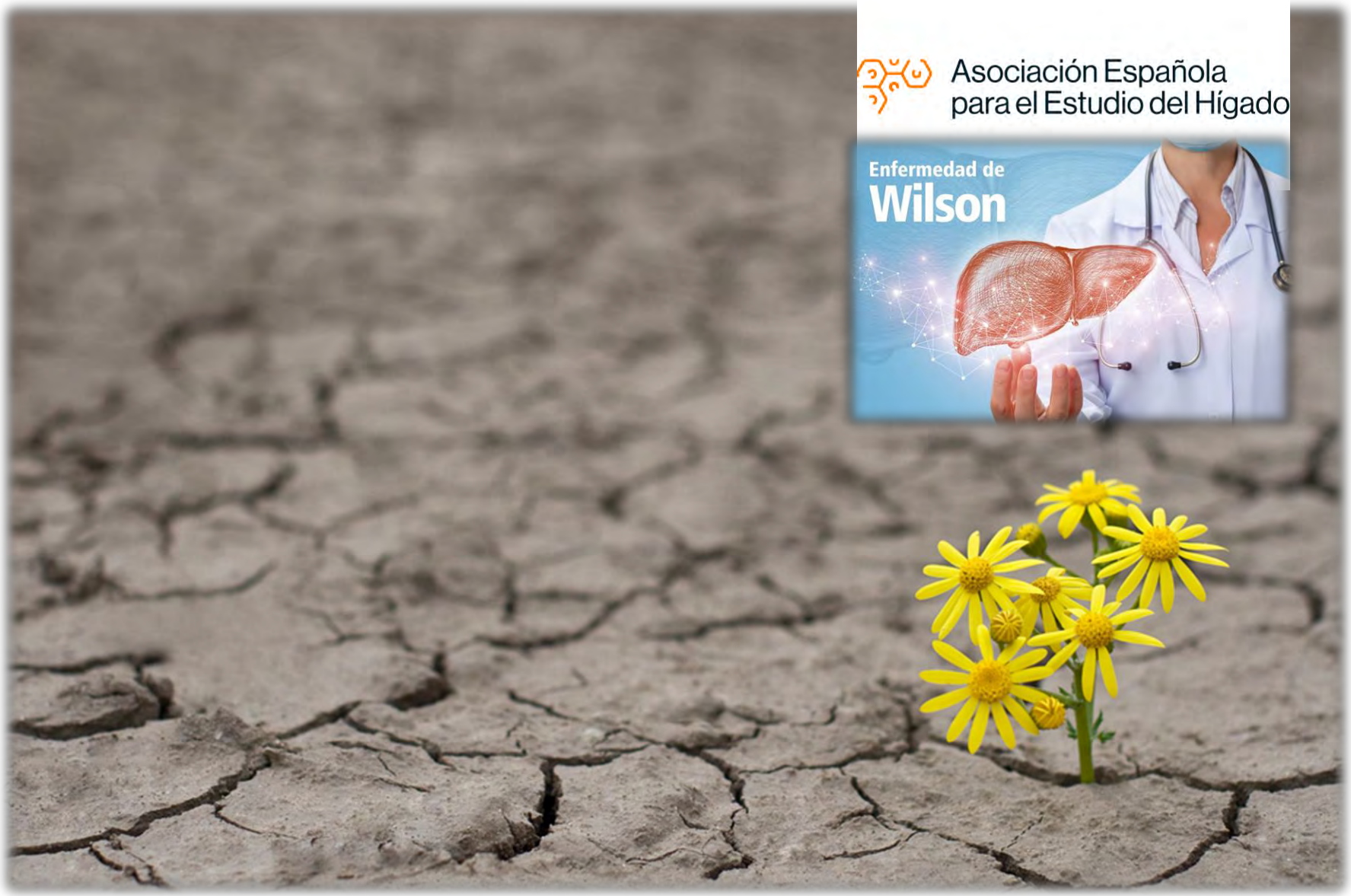
Patient Number	Sex	Age, years	Transplant	ALT, IU/L	AST, IU/L	ALP, IU/L	TB, mg/dL	INR	Albumin, g/dL	Creatinine, mg/dL	Lactate, mmol/L	Platelets, ×1000/ mm^3	Hb, g/dL
1	Male	19	No	48	77	47	4.9	2.3	2.2	NA	NA	119	7.6
2	Male	19	No	52	102	90	4.9	2.6	2	0.55	NA	77	9
3	Female	49	No	714	585	46	9.5	2.4	1.9	0.7	1.3	159	12.5
4	Female	57	Yes	44	198	39	10.42	2.17	2.2	0.6	1.8	106	10.2
5	Female	21	Yes	16	83	25	35	2.5	2.4	0.6	NA	173	8.2
6	Female	18	Yes	20	125	24	48.1	2.8	2.8	0.82	1.7	195	5.7
7	Female	25	Yes	255	364	184	16.7	3.7	2	0.63	NA	46	9.7
8	Female	20	Yes	52	181	44	11.7	5.4	1.4	0.53	NA	88	9.1

Patient Number	Leipzig Score*	K-F Rings	Ceruloplasmin, mg/dL	24-Hour Urine Copper, µg	ATP7B Mutation Analysis†	Hemolytic Anemia‡	Liver Copper, µg/g dry weight of liver
1	6	Yes	4	7583	NA	NA	NA
2	7	No	16	3235	Homozygous	NA	NA
3	5	Inconclusive	17	146	1 exon loci	NA	70
4	5	Yes	23	NA	NA	Yes	1122
5	8	Yes	4	4702	Heterozygous	Yes	NA
6	6	No	13	17,210	NA	Yes	1525
7	10	No	9	3991	Homozygous	NA	1374
8	8	Yes	9	1094	NA	Yes	§





Enfermedad de Wilson



jampuero-ibis@us.es

@Dr_Ampuero