MÁSTER EN HEPATOLOGÍA

Universidad Autónoma de Madrid

Universidad de Alcalá

Asignatura: Hepatitis Virales

"Manifestaciones extrahepáticas en la infección por Hepatitis Virales"

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Manifestaciones extrahepáticas en la infección por hepatitis virales

Casa de salud Valdecilla,1929

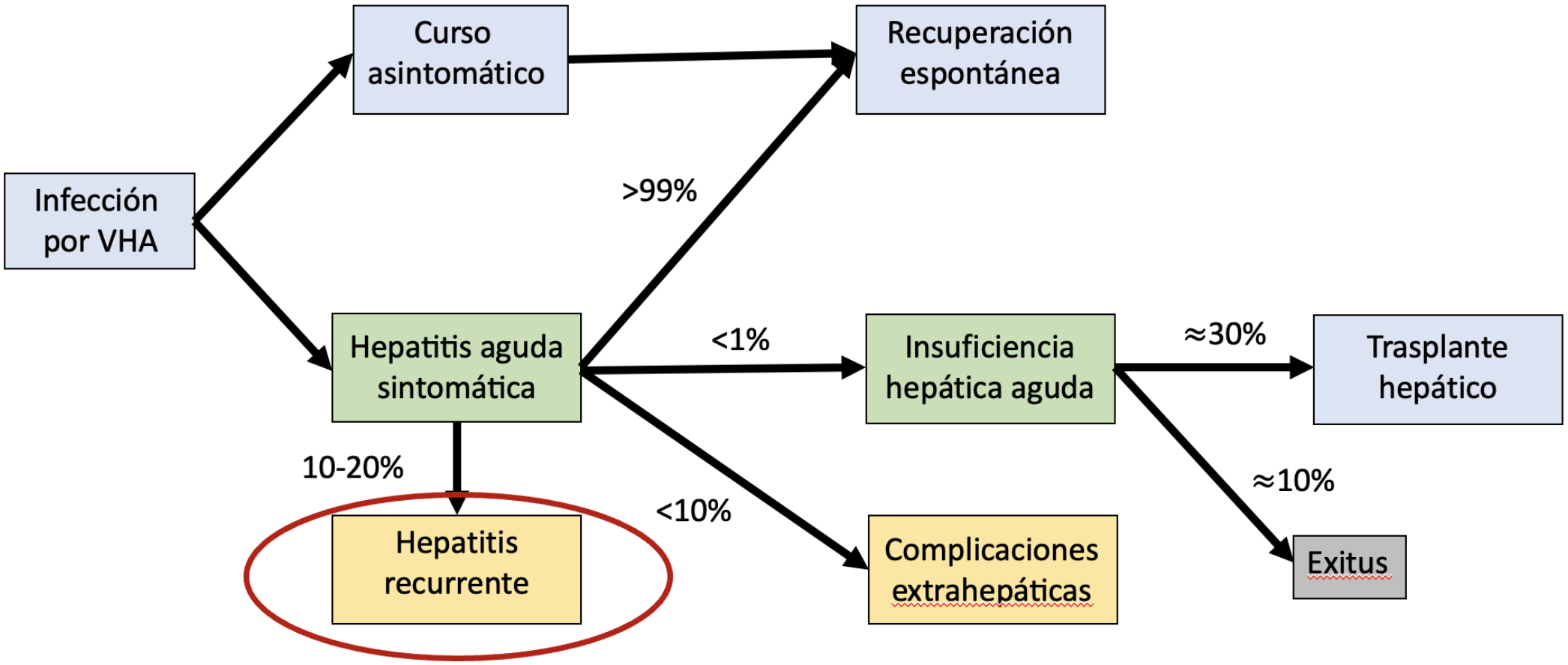
Manifestaciones extrahepáticas en la infección por hepatitis virales
Conceptos básicos

La historia natural de **todas** las hepatitis virales demuestra que son capaces de inducir manifestaciones manifestaciones extrahepáticas.

Estas manifestaciones extrahepáticas se pueden producir tanto durante la **fase aguda de la enfermedad**, como, en los casos en los que la hepatitis viral es capaz de inducir una hepatitis crónica, en la **fase crónica de la enfermedad.**

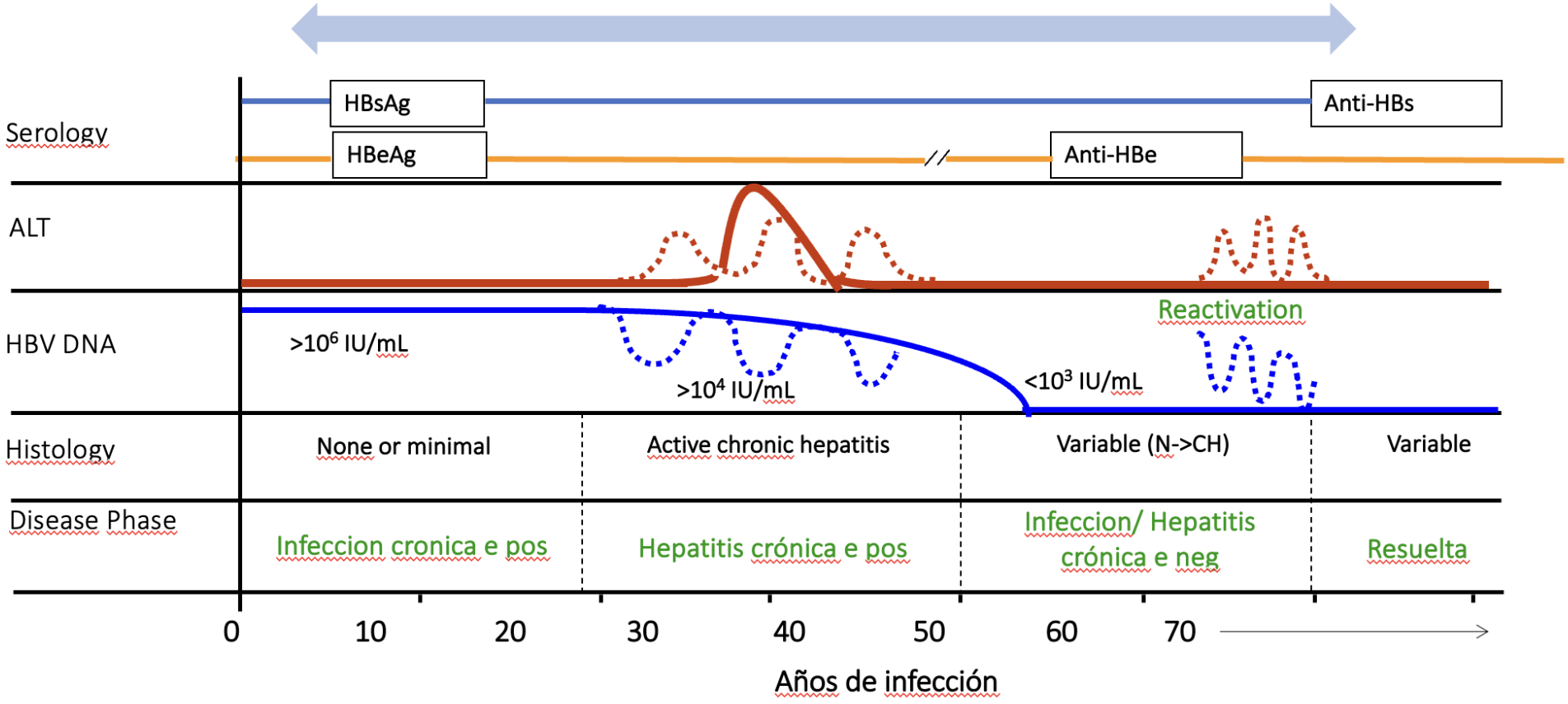
No existe un mecanismo común que permita explicar todas las manifestaciones extrahepáticas.

Manifestaciones extrahepáticas de la hepatitis A
Historia natural del VHA



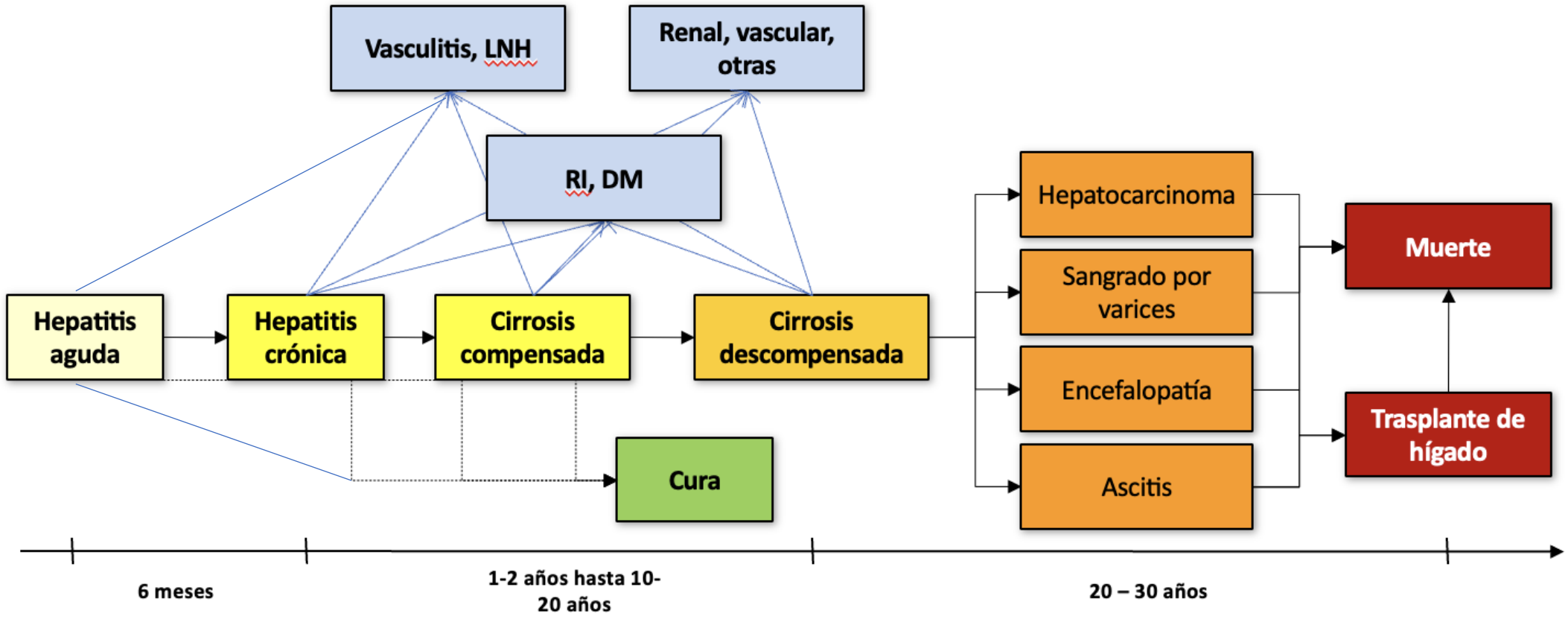
Manifestaciones extrahepáticas de la hepatitis B
Historia natural del VHB

*Progresión de la hepatitis crónica B es típicamente **dinámica, no secuencial** y potencialmente **bidireccional**.*



Manifestaciones extrahepáticas de la hepatitis B

Manifestaciones extrahepáticas de la hepatitis C
Historia natural del VHC



Manifestaciones extrahepáticas de la hepatitis E
Historia natural del VHE

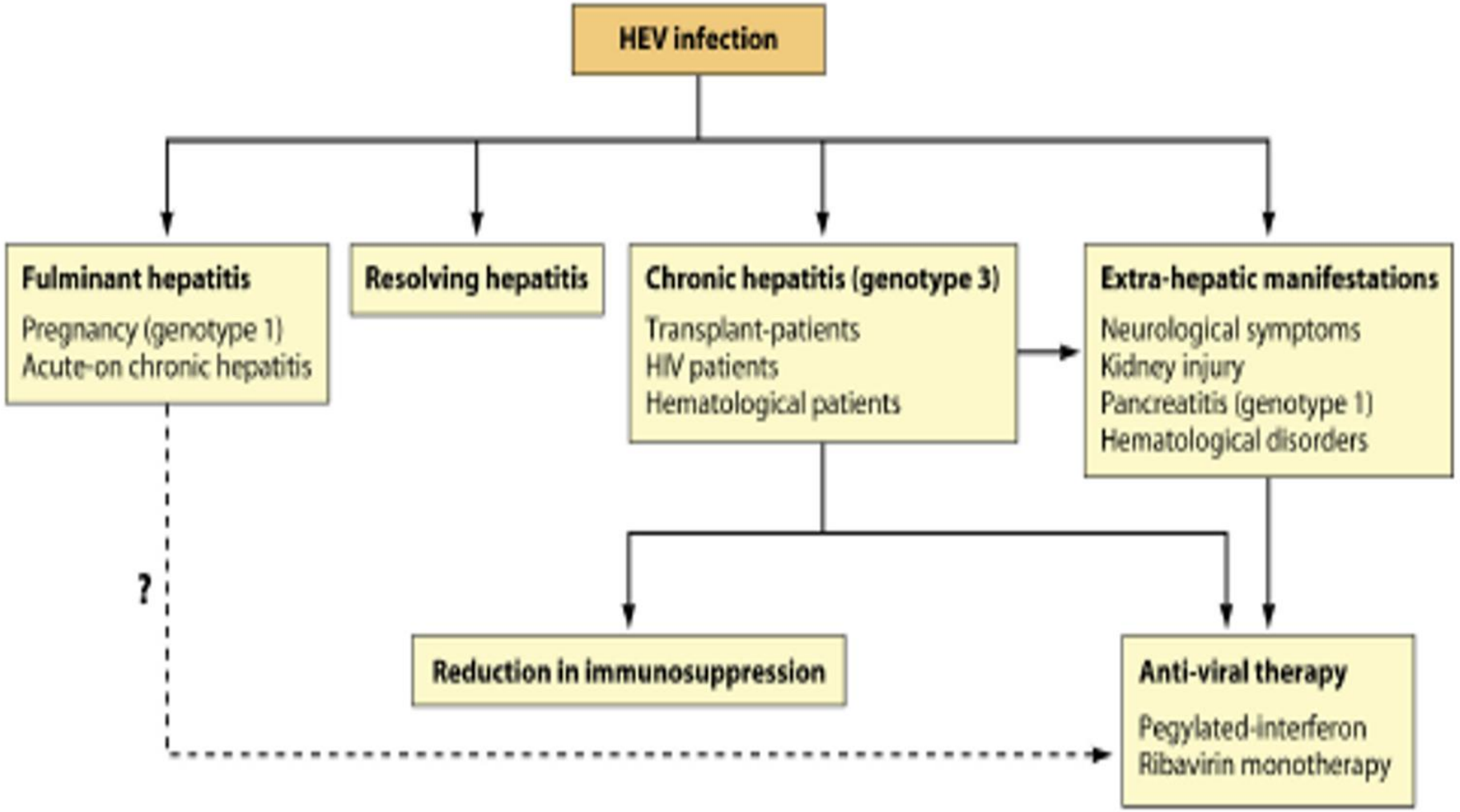


FIG 5 Different patterns of hepatitis E virus infection.

Kamar et al. Clin Microbiol Rev 2014: 27: 116-138

Manifestaciones extrahepáticas en la infección por hepatitis virales
Conceptos básicos

Aunque, como hemos dicho, **no existe un mecanismo común** que permita explicar todas las manifestaciones extrahepáticas, la existencia de mecanismos de base inmunológica es muy frecuente.

Y un segundo mecanismo relativamente frecuente, es consecuencia de la infección de células mononucleares por parte de algunos virus de la hepatitis **(VHB / VHC).**

Manifestaciones extrahepáticas de la hepatitis A
Historia natural del VHA

- **Crioglobulinemia:** **Vasculitis leucocitoclástica**
- **Glomerulonefritis**
- **Artritis**
- **Miocarditis**
- Necrolisis epidérmica tóxica
- **Neuritis óptica, mielitis transversa, síndrome Guillain-Barré**
- Trombopenia / **Anemia hemolítica autoinmune** / Leucopenia/ anemia aplásica

La presencia de hepatitis A puede ser el desencadenante de HAI tipo I. Posible defecto en linfocitos T supresores encargados del control de la respuesta inmune al receptor de asialoglicoproteína.

Webb et al. Clinical Micro (2020)

Manifestaciones extrahepáticas de la hepatitis B
Hepatitis aguda / crónica

Acute HBV infection

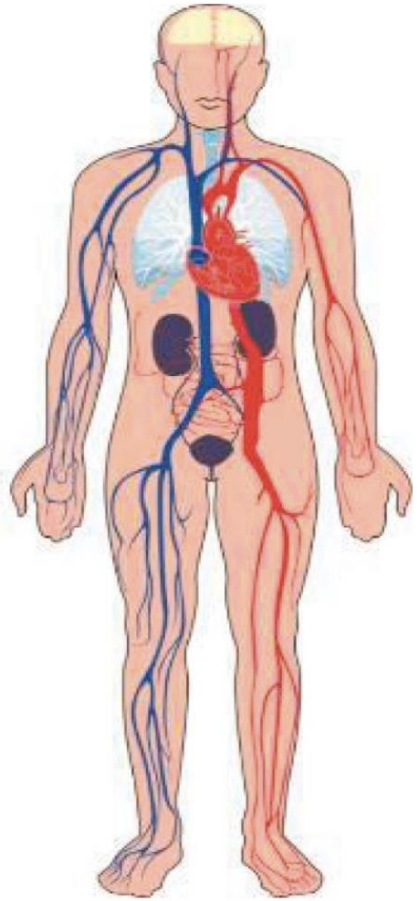
Systemic
- Flu-like syndrome
- Serum sickness
- Polyarteritis nodosa *
- Cryoglobulinemia *

Rheumatological
- Polyarticular joint pain
- Polyarticular arthritis

Skin
- Papular acrodermatitis of childhood
- Acute urticarial
- Leukocytoclastic vasculitis

Renal
- Membranous glomerulonephritis *

Neurological
- Polyradiculoneuritis



Chronic HBV infection

Reduced quality of life*

Ophthalmological
- Uveitis

Hematological
- Non-Hodgkin's lymphoma

Skin
- Oral lichen planus
- Pitted keratolysis
- Rheumatoid purpura

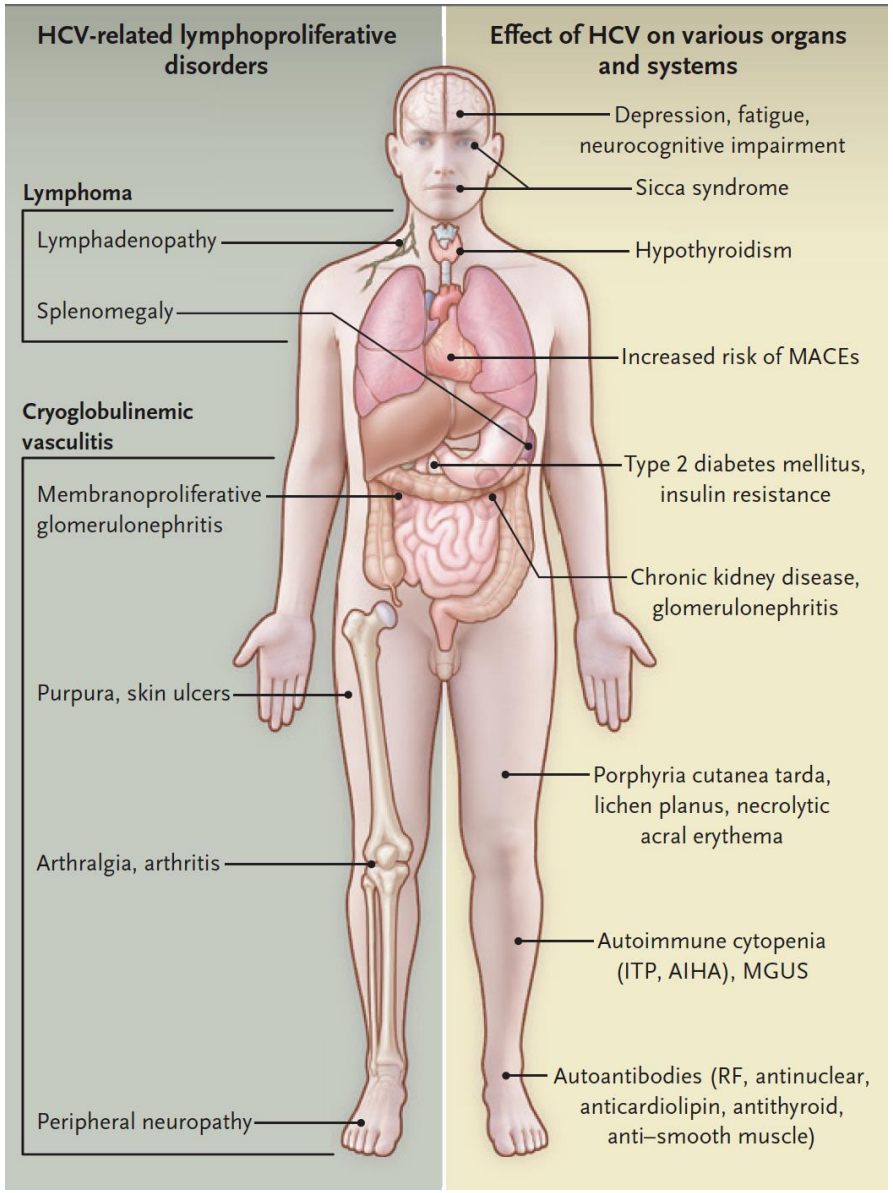
Renal
- Membranoproliferative glomerulonephritis *
- IgA nephropathy

Autoantibodies
- Anti-smooth muscle, anti-nuclear, anti-SSA/SSB

* Efficacy of HBV nucleos/tide analogues

Am J Gastroenterol 2022;117:253–263. https://doi.org/10.14309/ajg.0000000000001575

Manifestaciones extrahepáticas de la hepatitis C
Un vistazo general



Consecuencias clínicas

Curación enfer. hepática

Curación enfer. Extrahepática

Consecuencias Salud Pública

Disminución reinfección
Eliminación
Aumento recursos para otros pacientes

Consecuencias percibidas por el paciente

Calidad de vida
Productividad
Neurocognitivo

Consecuencias Económicas

QUALYs
Haciendas

N Engl J Med 2021;384:1038-52. / DOI: 10.1056/NEJMra2033539

Manifestaciones extrahepáticas de la hepatitis E
Manifestaciones documentadas

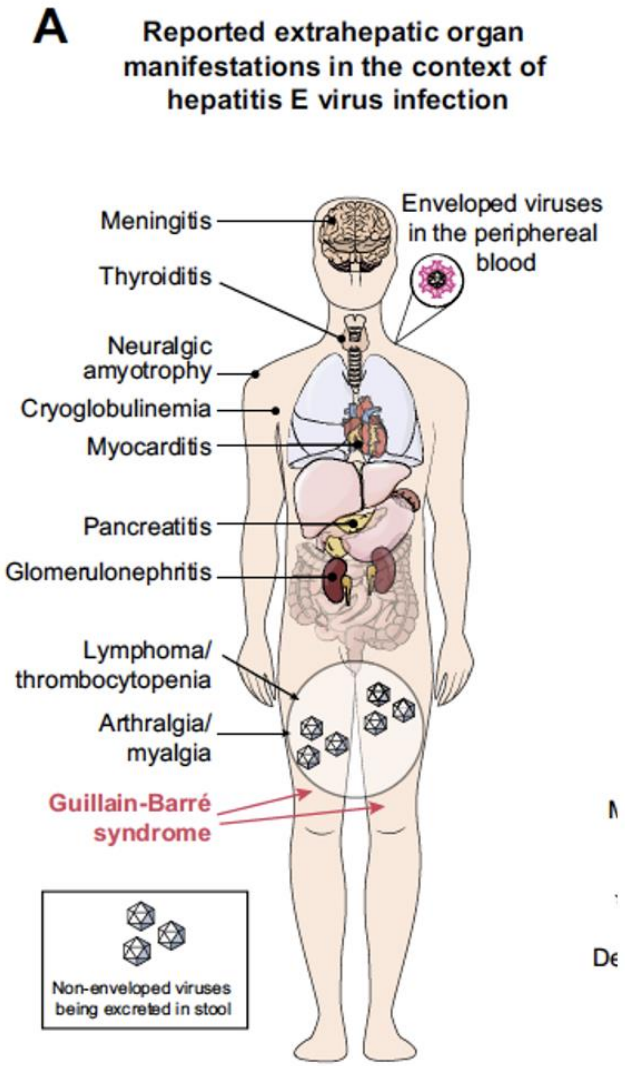


Table 1. Likelihood of causal relationship between HEV infection and assumed extrahepatic manifestation.

Assumed extrahepatic manifestation	Current data	Hill's criteria	Estimated likelihood of causal relationship
Neuralgic amyotrophy	• Acute HEV infection in 11% of NA patients • HEV replication in neuronal cells proven (*in vitro*)	• Strong association, temporality • Experimental	Very probable
Guillain-Barré syndrome	• Acute HEV infection in 10% of GBS patients from India and 5% from the Netherlands • HEV replication in neuronal cells proven (*in vitro*) • Typical post-infectious condition	• Strong association, temporality, consistency (consistent findings in two independent cohorts) • Experimental • Plausibility	Very probable
Cryoglobulinemia	• 9/10 during HEV infection • Elevated anti-HEV seroprevalence rate in patients with idiopathic cryoglobulinemia • Similar mechanisms described for HCV	• Temporality • Plausibility	Possible
Glomerulonephritis	• 9/51 patients with renal impairment during chronic HEV infection • Similar mechanisms described for HCV • Evidence from various experimental data	• Strong association, • Plausibility • Experimental	Very probable
Acute pancreatitis	• Large number of reports from HEV-GT1 region describing AP shortly after the diagnosis of acute HEV infection • Known for other viral infections, e.g., HAV/HBV/HCV-infection	• Temporality, consistency • Plausibility	Very probable
Hematological diseases	• Several cases observed. • High incidence of MGUS during HEV infection in a single study (However, it is possible that underlying haematological disease made patients susceptible for HEV infection)	• Strong association	Possible
Meningitis	• HEV detection in CSF • HEV replication in neuronal cells proven	• Temporality, plausibility • Experimental	Possible
Autoimmune hepatitis	• Elevated anti-HEV seroprevalence rate in AIH patients		Under debate
Thyroiditis	• Only single case reports		Doubtful
Myocarditis	• Single cases • Only one single small study, which did not observe an association		Doubtful

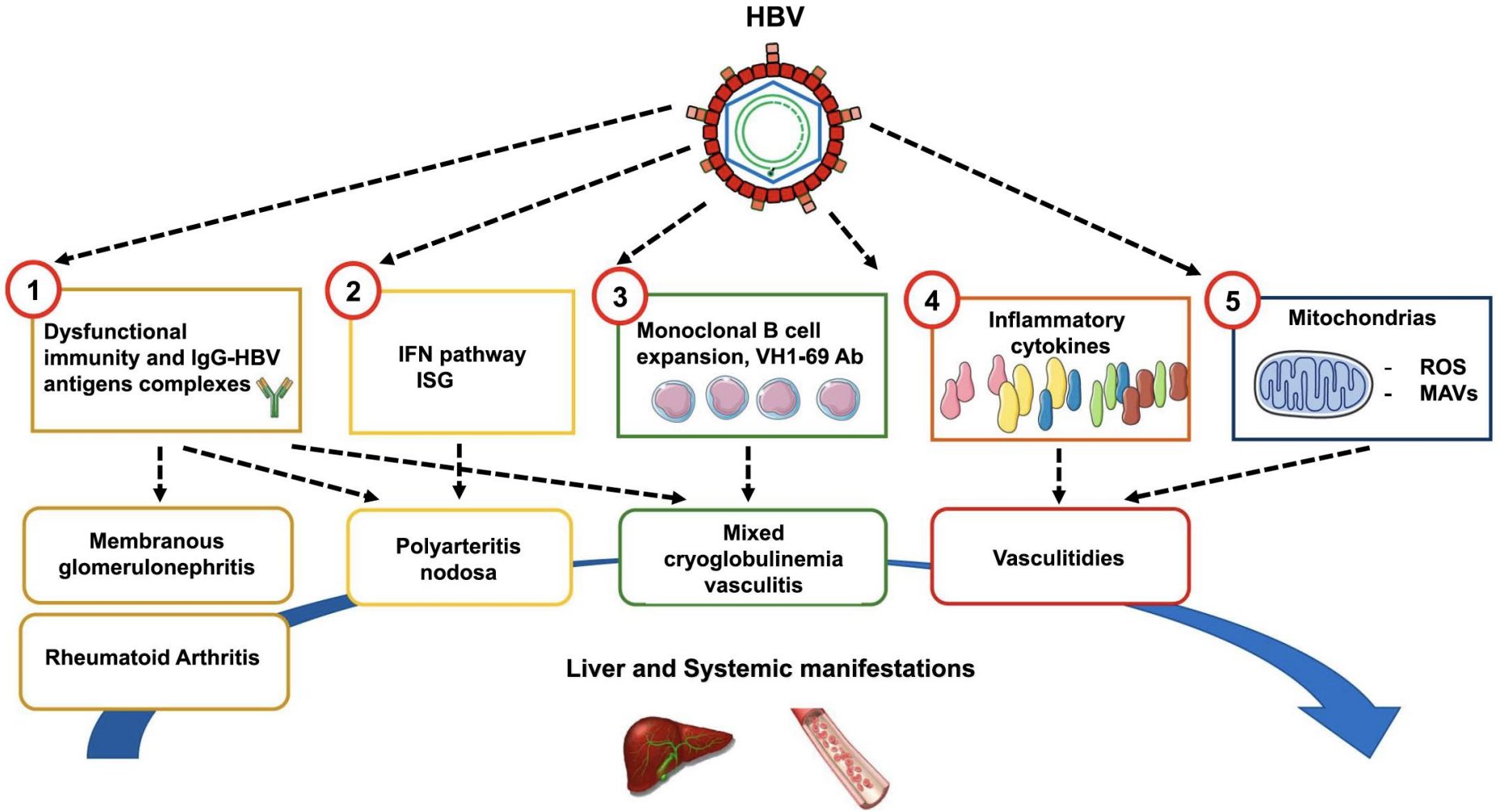
Pischke S et al J Hepatol 2017

Manifestaciones extrahepáticas en la infección por hepatitis virales

Conceptos básicos

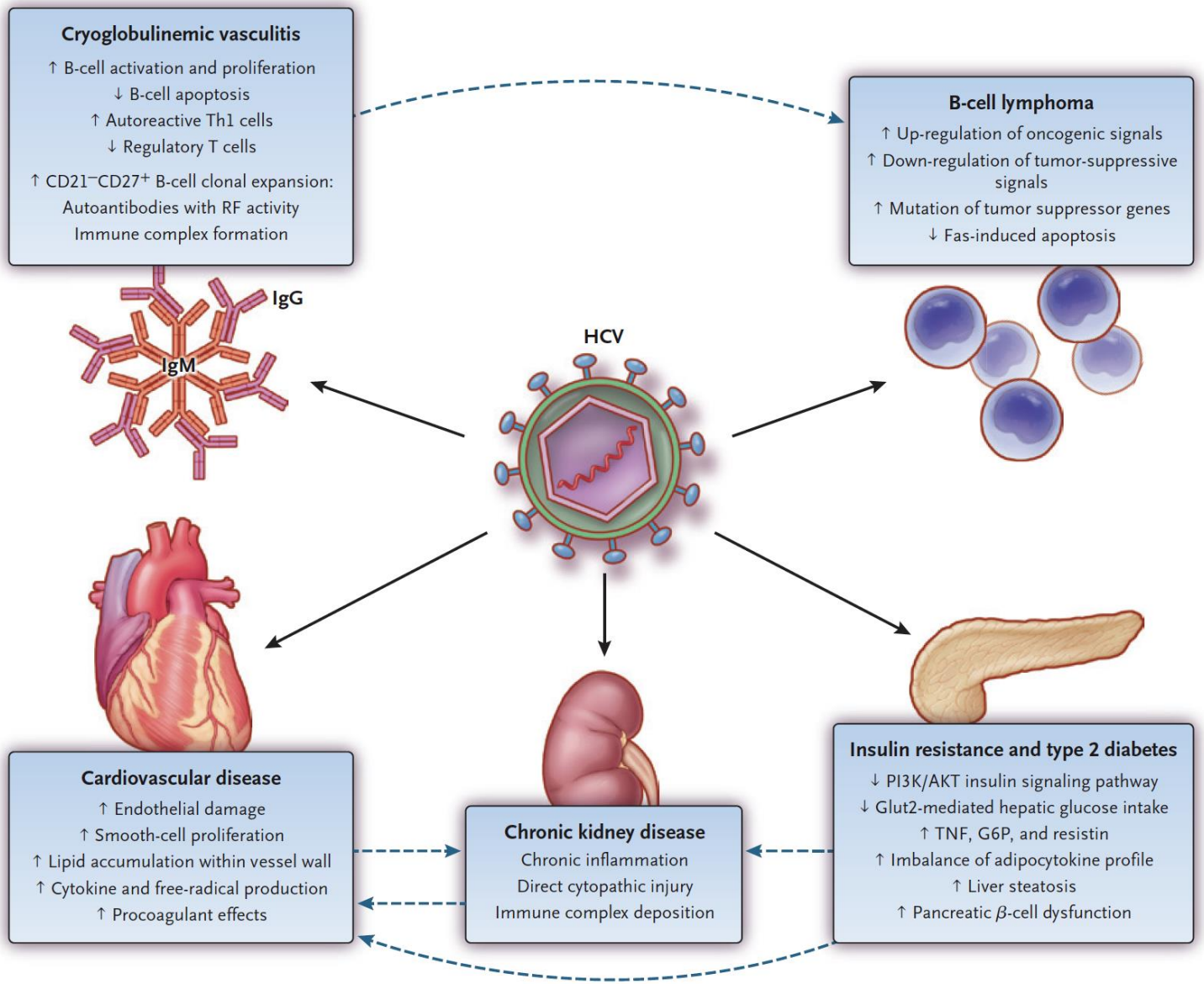
A pesar de existir puntos en común como ya hemos destacado (inmunológicos) existen diferentes mecanismos patogénicos, particularmente estudiados en las infecciones por los virus de la hepatitis B y C.

Manifestaciones extrahepáticas de la hepatitis B
Hepatitis aguda / crónica



Am J Gastroenterol 2022;117:253–263. https://doi.org/10.14309/ajg.0000000000001575

Manifestaciones extrahepáticas de la hepatitis C
Fisiopatología



N Engl J Med 2021;384:1038-52. /
DOI: 10.1056/NEJMra2033539
J Hepatology 2016; 65: S82-S94

Manifestaciones extrahepáticas en la infección por hepatitis virales

Conceptos básicos

En general, no existe ninguna relación entre el grado de replicación viral y el desarrollo o gravedad de las manifestaciones extrehepáticas.

Este hecho dificulta su reconocimiento y la relación etiológica con la propia hepatitis viral.

Manifestaciones extrahepáticas de la hepatitis C

Un vistazo general

Class A Significant prevalence, consistent pathogenetic data, "ex adjuvantibus" criteria	Class B Higher prevalence compared with controls	Class C Possible association	Class D Anecdotal association	Class E Association with interferon-α therapy
Mixed cryoglobulinemia	Type 2 diabetes Insulin resistance	Polyarthritis	Polymyositis	Hypo-hyperthyroidism
Cryoglobulinemic vasculitis	Cardiovascular disease	Pruritus	Dermatomyositis	Depression
B-cell non-Hodgkin lymphoma	Glomerulonephritis	Fibromyalgia	Polyarteritis nodosa	Fatigue
	Renal insufficiency Fatigue	Chronic polyradiculoneu-ropathy	Psoriasis	Sarcoidosis
	Cognitive impairment	Lung alveolitis	Mooren corneal ulcer	Lichen
	Depression		Erythema nodosum	Skin vasculitis
				Peripheral neuropathy

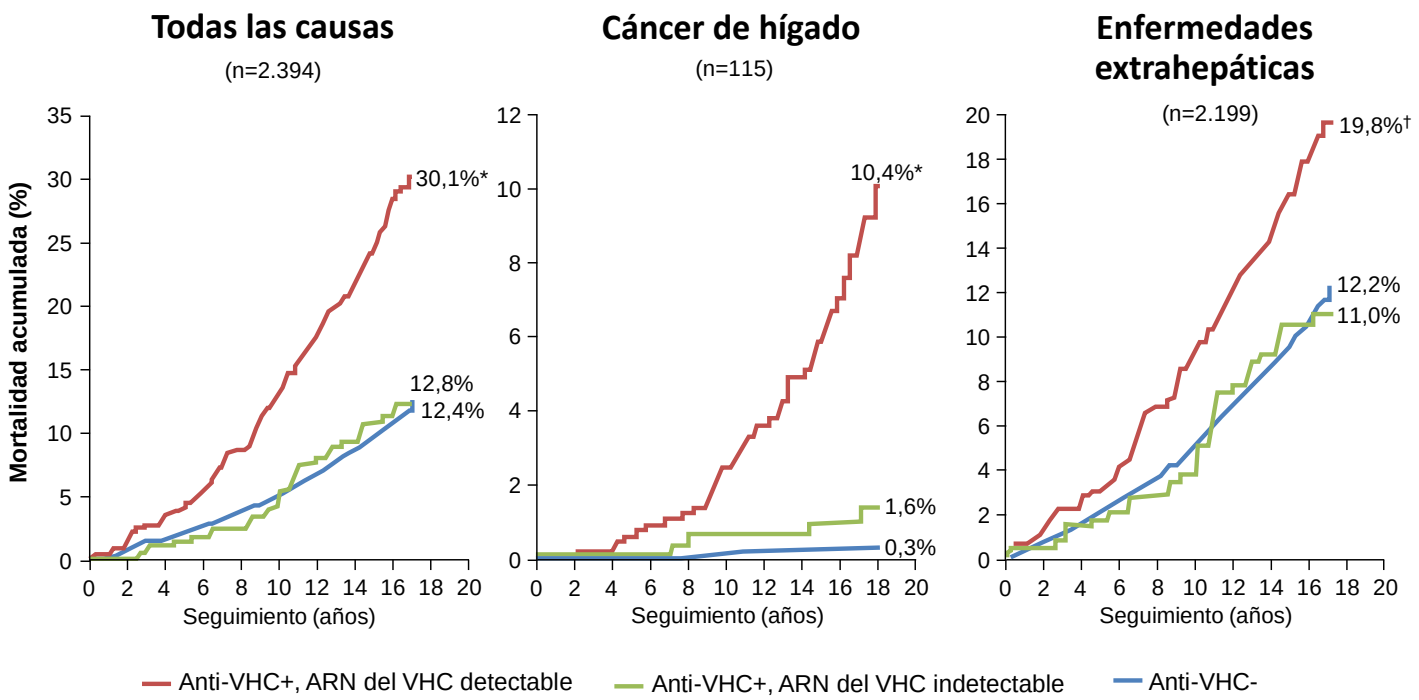
Manifestaciones extrahepáticas en la infección por hepatitis virales

Conceptos básicos

Las manifestaciones extrahepáticas incrementan la morbimortalidad atribuible a estas enfermedades

Manifestaciones extrahepáticas de la hepatitis C
Eficacia de la terapia antiviral

La infección crónica por VHC aumenta la mortalidad por enfermedades hepáticas y extrahepáticas



*P<0,001 para la comparación entre los 3 grupos y P<0,001 para ARN del VHC detectable frente a indetectable; †P<0,001 para la comparación entre los 3 grupos y P=0,002 para ARN del VHC detectable frente a indetectable

Lee MH et al. J Infect Dis 2012;206:469–77

El riesgo de desarrollar vasculitis crioglobulinémica y linfoma de células B no linfoma no Hodgkin de células B (LNHB) fue menor en los pacientes que tuvieron una respuesta virológica sostenida que en los que no la tuvieron. respuesta virológica sostenida que en los que no la tuvieron. Una respuesta virológica sostenida a los respuesta virológica sostenida a los primeros regímenes terapéuticos también redujo el riesgo de síndrome coronario agudo, enfermedad cardiovascular, resistencia a la insulina y diabetes de tipo 2.

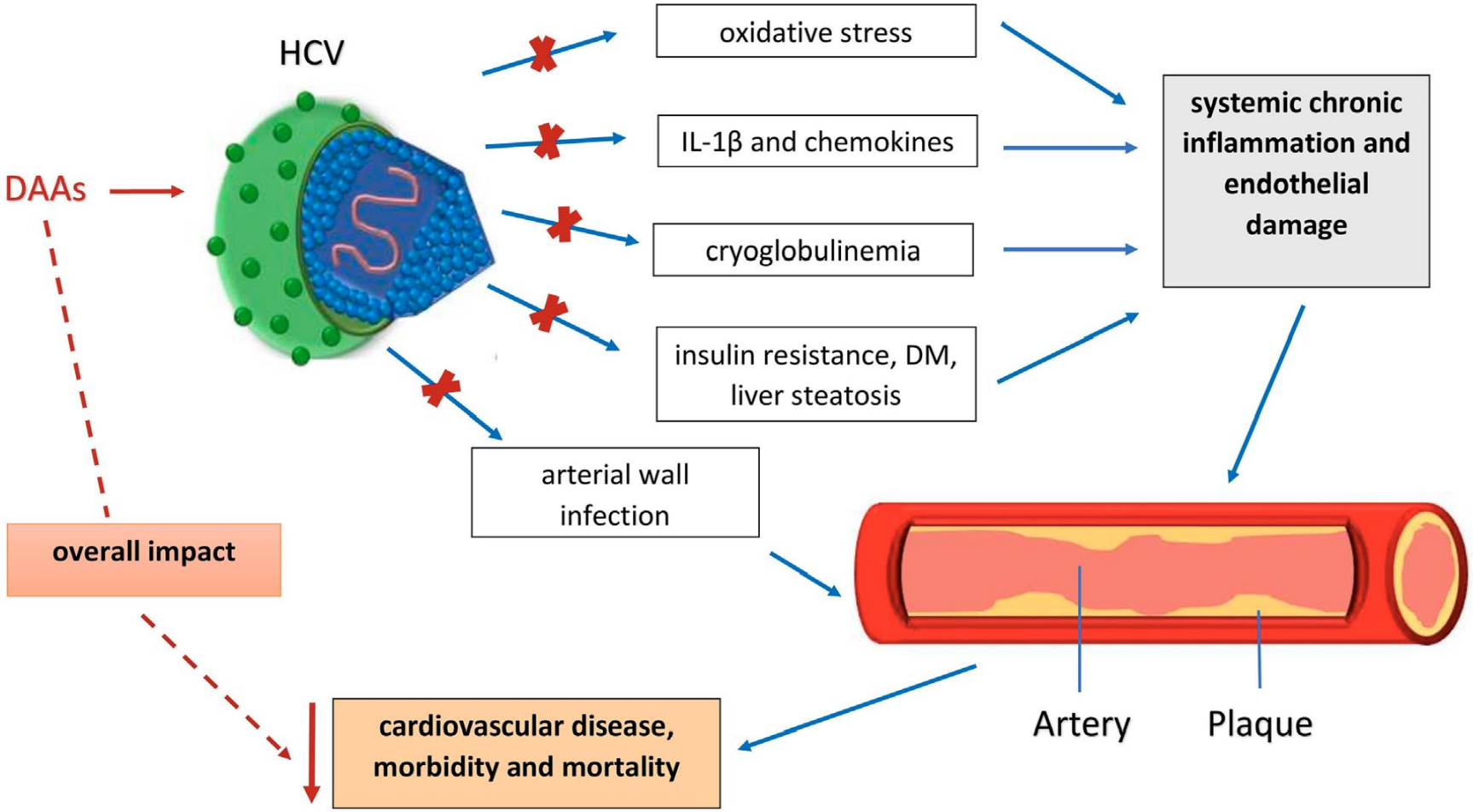
Mahale P, et al. Gut 2018; 67: 553-61.
Hsu Y-C, et al. Gut 2015; 64: 495-503.
5. Innes HA, et al. Hepatology 2015; 62: 355-64.
6. Cacoub P, et al. Gut 2018; 67: 2025-34.

Manifestaciones extrahepáticas en la infección por hepatitis virales

Conceptos básicos

El tratamiento antiviral mejora la mayor parte de las manifestaciones extrahepáticas.

Manifestaciones extrahepáticas de la hepatitis C
Eficacia de la terapia antiviral



Roguljic H, Nincevic V, Bojanic K, Kuna L, Smolic R, Vcev A, Primorac D, Vceva A, Wu GY and Smolic M (2021) Impact of DAA Treatment on Cardiovascular Disease Risk in Chronic HCV Infection: An Update. Front. Pharmacol. 12:678546. doi: 10.3389/fphar.2021.678546

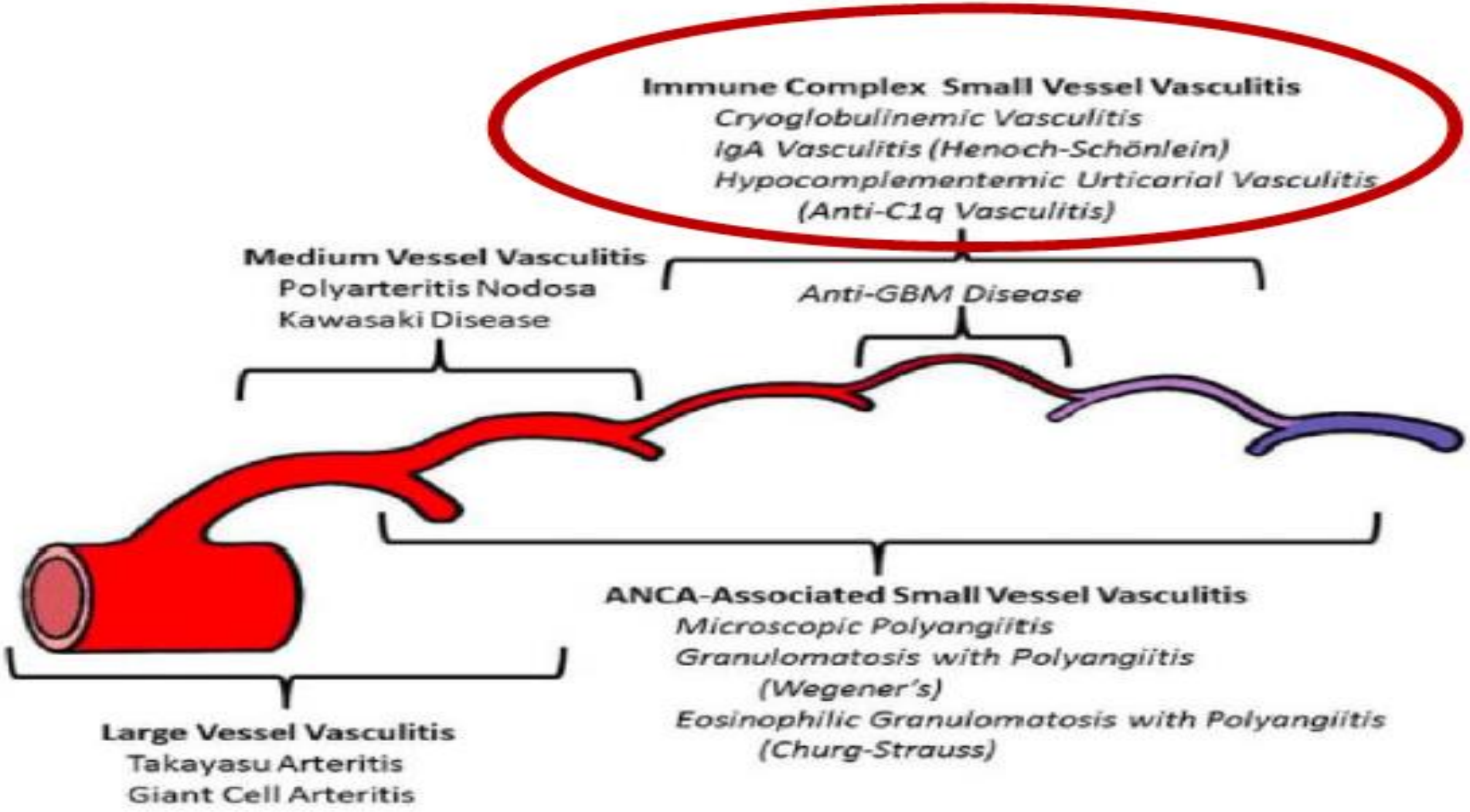
Manifestaciones extrahepáticas en la infección por hepatitis virales
Concepto de vasculitis

- **Concepto**
  - síndromes caracterizados por **inflamación** de los vasos sanguíneos (inflamación local)
  - puede haber activación inmunológica local y sistémica

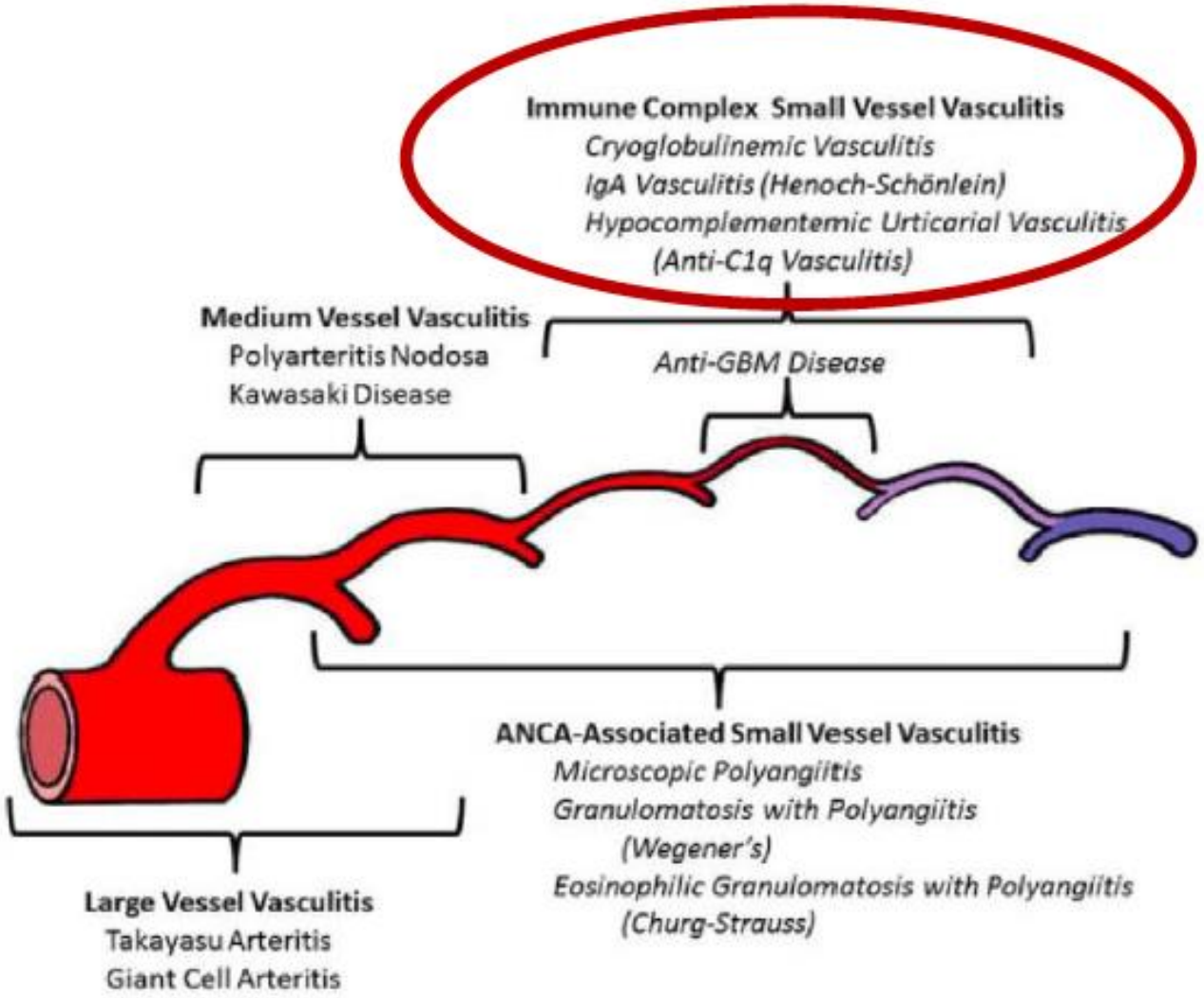
- **Clínica**
  - **Isquémica**
    - Por estenosis y/o oclusión de la luz vascular, dependen
      - extensión
      - tamaño de los vasos
      - localización
  - **Sistémica:** por inflamación focal y sistémica (citocinas)
    - fiebre, síndrome general
    - ↑ reactantes de fase aguda

Manifestaciones extrahepáticas en la infección por hepatitis virales

Concepto de vasculitis



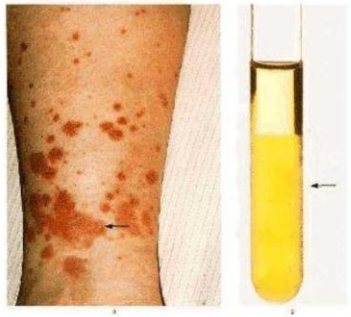
Manifestaciones extrahepáticas en la infección por hepatitis virales
Vasculitis de pequeño vaso por inmunocomplejos



- Vasculitis con marcado o moderado **depósito de Inmunoglobulinas y/o complemento** en las paredes vasculares
- **Arteriolas, capilares o vénulas y pequeñas arterias**.
- Producen con frecuencia **glomerulonefritis**
- El depósito de inmunocomplejos(IC) en la pared vascular da lugar a la activación del complemento, quimiotaxisde los neutrófilos y liberación de citoquinas que dañan la pared vascular.

Manifestaciones extrahepáticas de las hepatitis viral por VHC
Crioglobulinemia

Crioglobulinas: proteinas insolubles a Tª inferior a 37º se solubilizan al recalentar

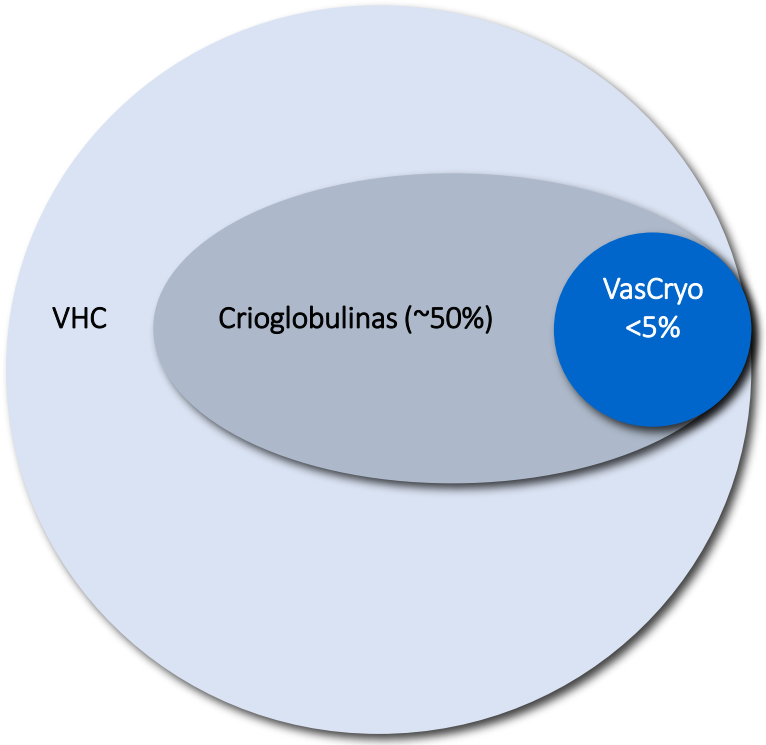


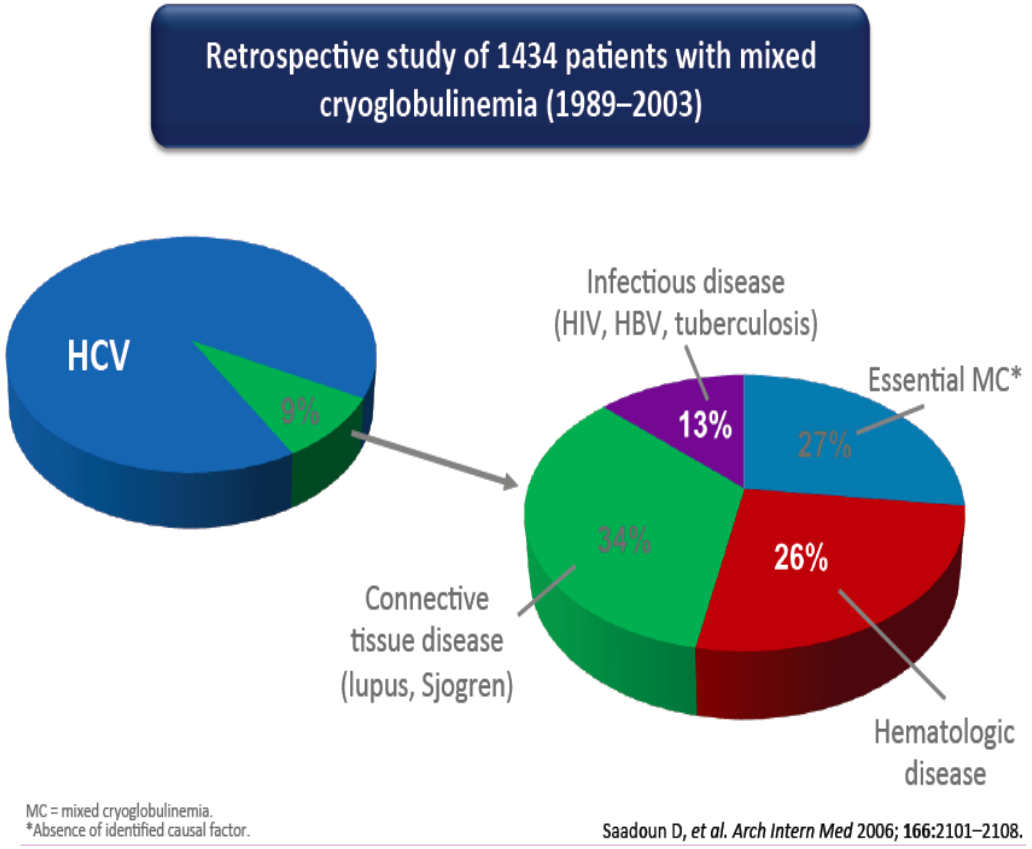
Tipo I: Solo **Inmunoglobulinas monoclonales IgM**
con menor frecuencia IgG o IgA o cadenas ligeras
Asociación a **Linfomas, macroglobulinemia de Waldenström, mieloma múltiple**

Tipo II: **Ig monoclonales con actividad FR**
Tipo III: **FR policlonal**

} Mixtas, asociación fundamental **VHC**
Idiopática

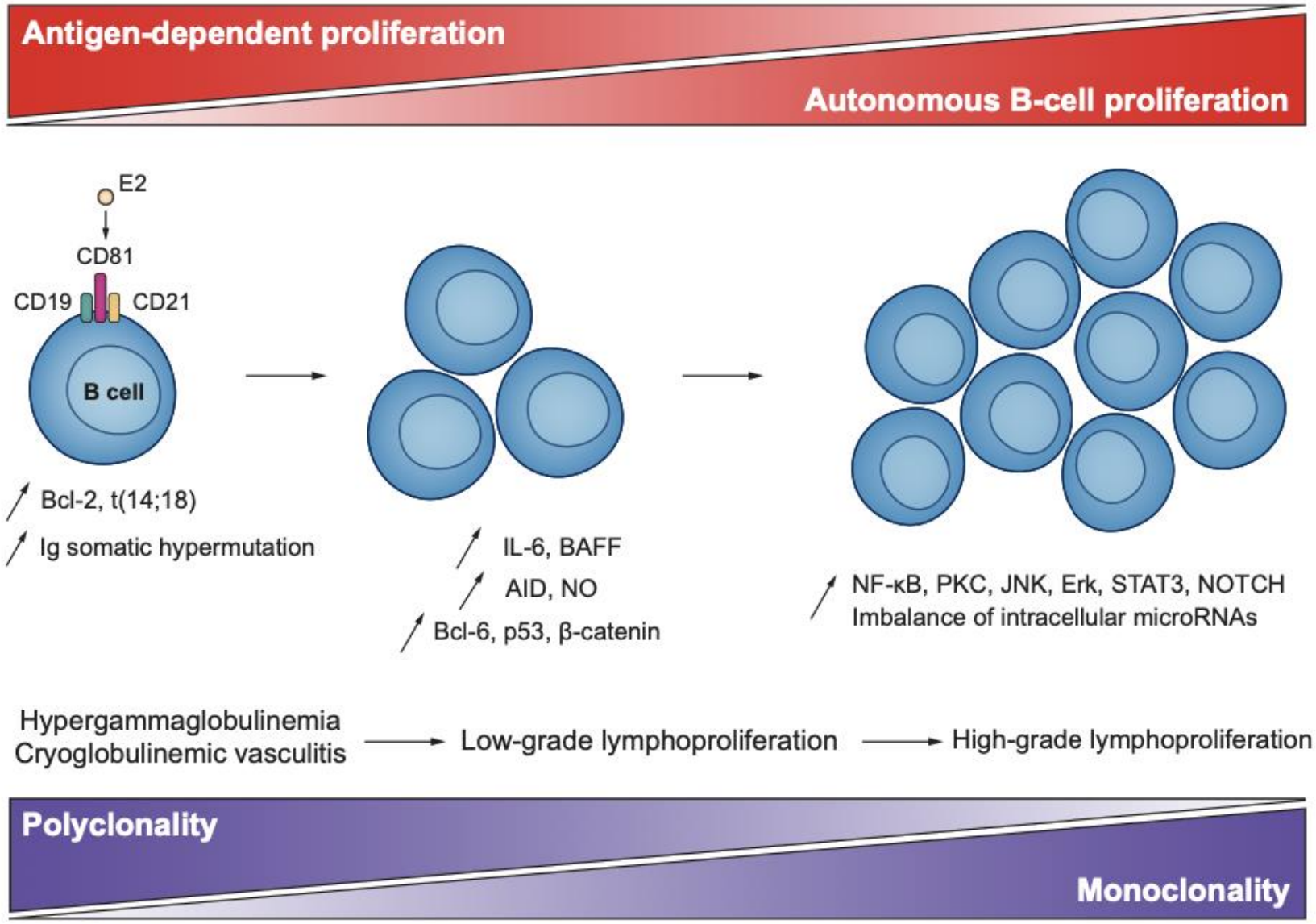
Manifestaciones extrahepáticas de las hepatitis viral por VHC
Crioglobulinemia





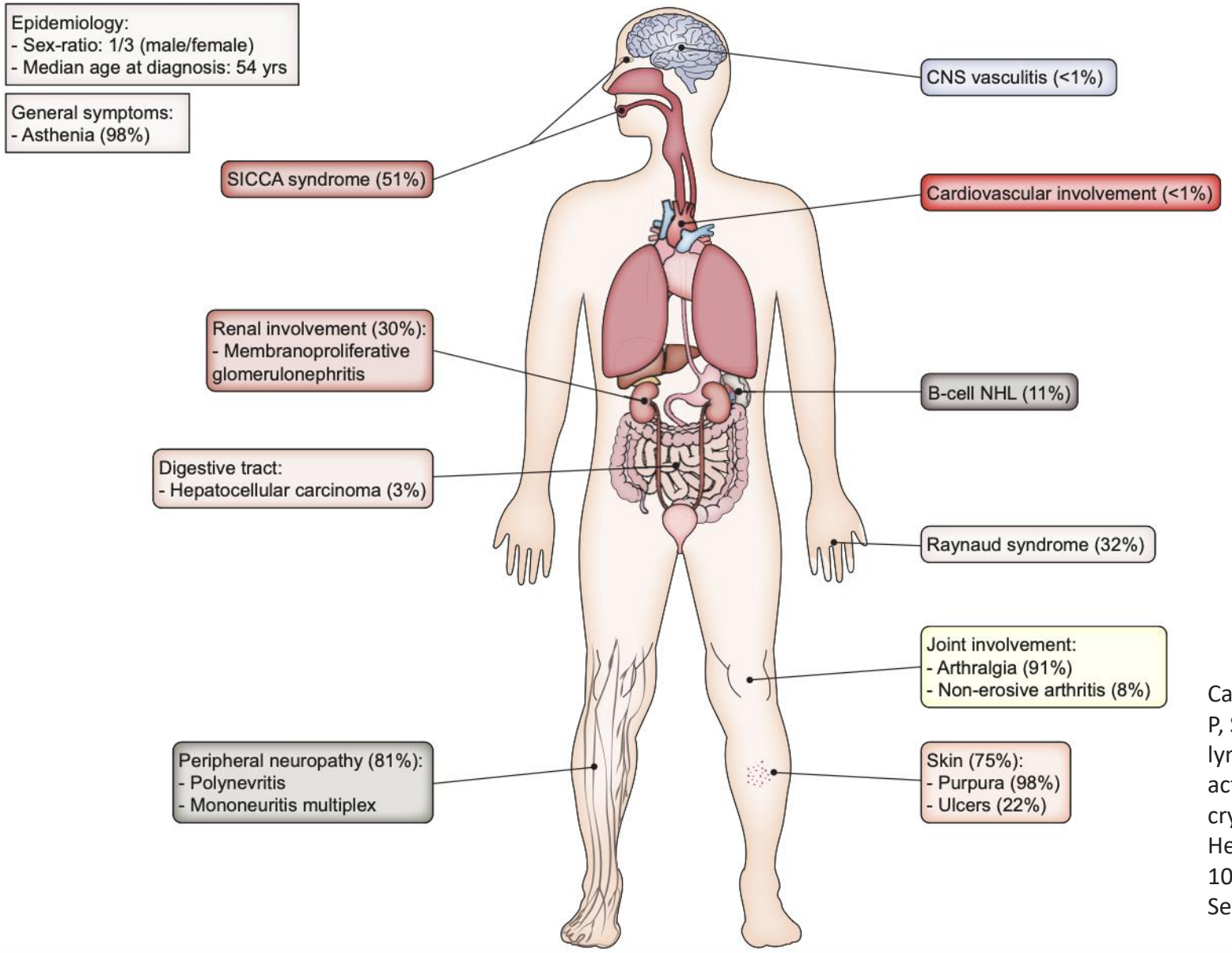
Ramos-Casals. Lancet 2012; 379: 348–60

Manifestaciones extrahepáticas de las hepatitis viral por VHC
LNH.



Cacoub P, Comarmond C, Vieira M, Régnier P, Saadoun D. HCV-related lymphoproliferative disorders in the direct-acting antiviral era: From mixed cryoglobulinaemia to B-cell lymphoma. J Hepatol. 2022 Jan;76(1):174-185. doi: 10.1016/j.jhep.2021.09.023. Epub 2021 Sep 29. PMID: 34600000.

Manifestaciones extrahepáticas de las hepatitis viral por VHC
Crioglobulinemia

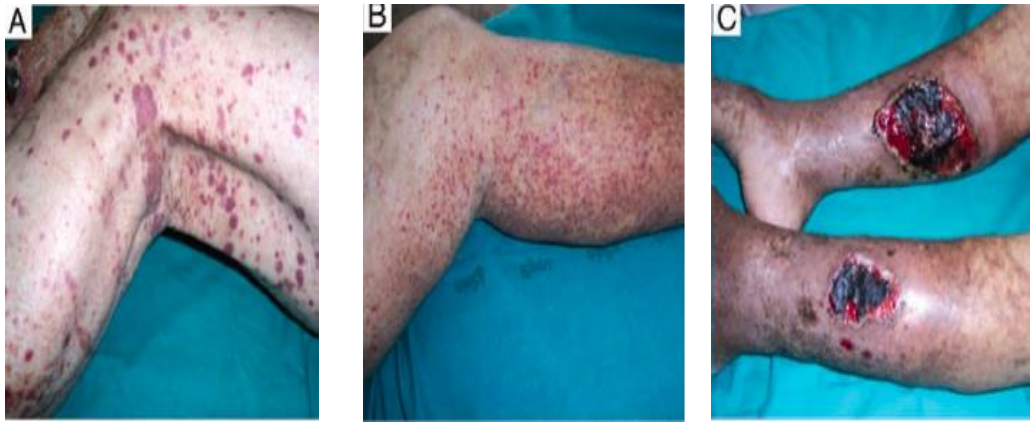


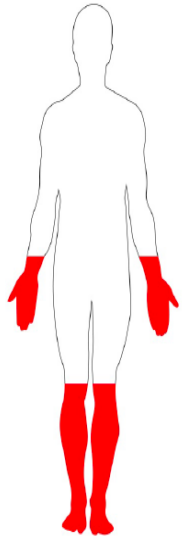
Cacoub P, Comarmond C, Vieira M, Régnier P, Saadoun D. HCV-related lymphoproliferative disorders in the direct-acting antiviral era: From mixed cryoglobulinaemia to B-cell lymphoma. J Hepatol. 2022 Jan;76(1):174-185. doi: 10.1016/j.jhep.2021.09.023. Epub 2021 Sep 29. PMID: 34600000.

Manifestaciones extrahepáticas de las hepatitis viral por VHC

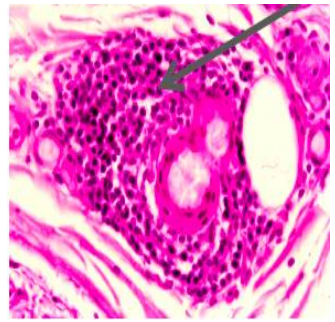
Crioglobulinemia

	%
Púrpura	98
Astenia	98
Artralgias	91
Polineuropatía periférica	81
Alteración PFH	73
Síndrome seco	51
Fenómeno de Raynaud	32
Afectación renal	31
Linfoma NH asociado	11
Artritis no erosiva	8
Hepatocarcinoma	3





PN axonal, simétrica, crónica, progresiva, sensitiva y dolorosa.



Infiltrado perivascular linfocítico

Cacoub P et al. Am J Med 2015 / Cacoub P et al. Dig Liv Dis 2014 / Damaco et al. NEJM 2013.
Dedania B et al. J Clin Transl Hepatol 2015 / Ferri C et al. WJH 2015

Manifestaciones extrahepáticas de las hepatitis viral por VHC

Crioglobulinemia

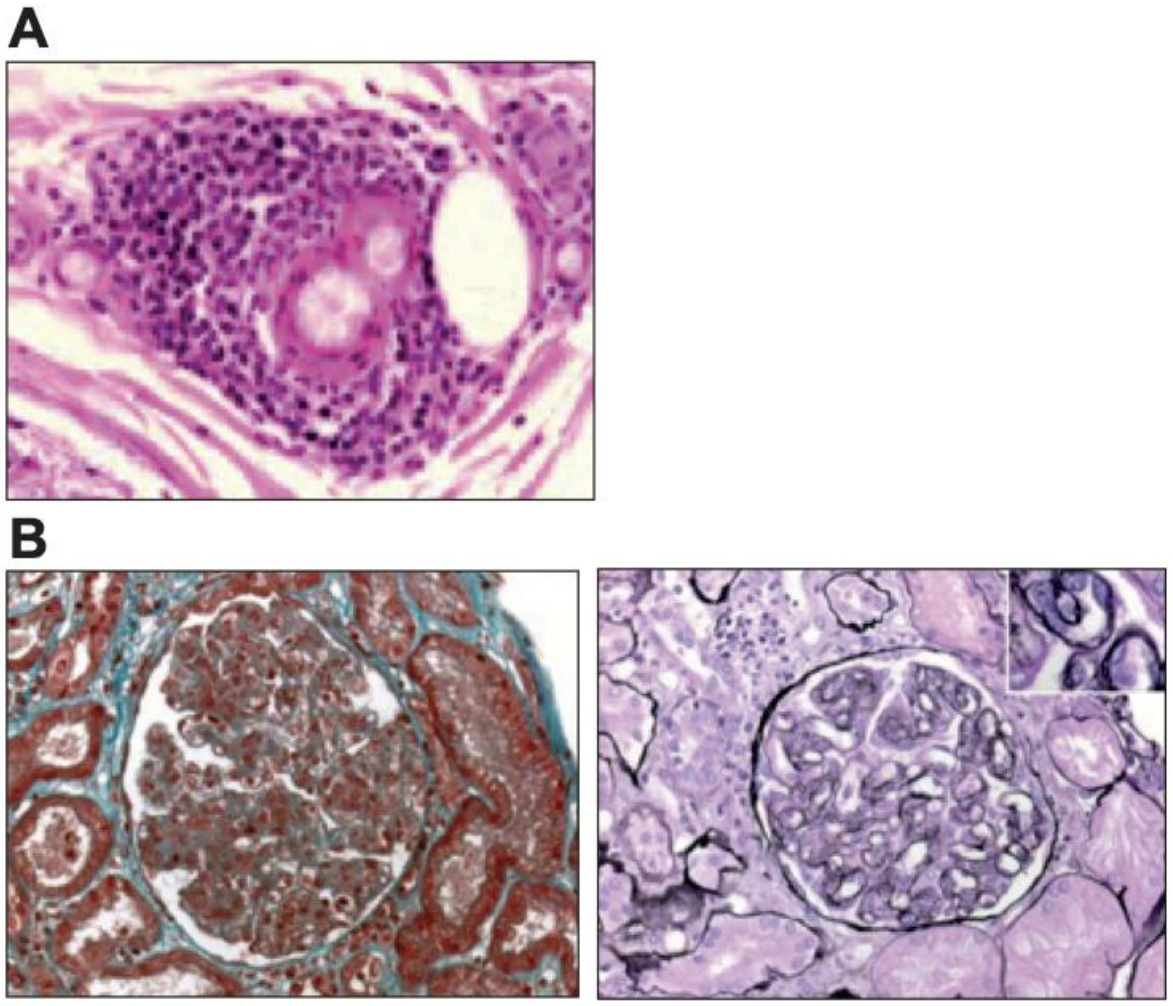
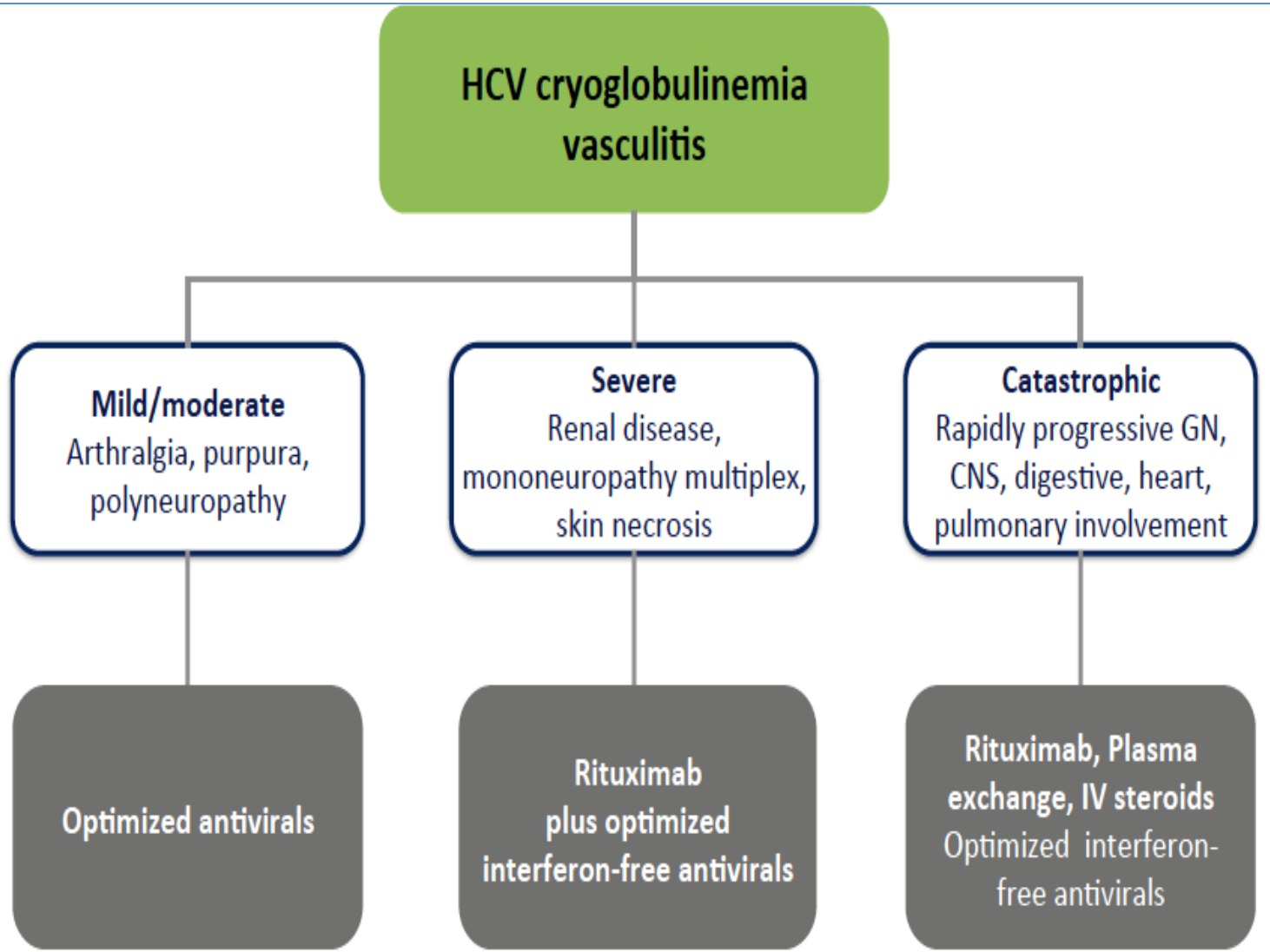


Fig. 2. HCV-cryoglobulinaemic vasculitis pathology. (A) Peripheral nerve biopsy showing a large perivascular infiltrate of Th1 lymphocytes located around small vessels (*i.e.*, venules, capillaries); of note is the absence of polymorphonuclear cells or destruction of the vascular wall. (B) Kidney biopsy showing membranoproliferative glomerulonephritis using optical microscopy (left) and electron microscopy (right). Th1, type 1 T helper.

Cacoub P, Comarmond C, Vieira M, Régnier P, Saadoun D. HCV-related lymphoproliferative disorders in the direct-acting antiviral era: From mixed cryoglobulinaemia to B-cell lymphoma. J Hepatol. 2022 Jan;76(1):174-185. doi: 10.1016/j.jhep.2021.09.023. Epub 2021 Sep 29. PMID: 34600000.

Manifestaciones extrahepáticas de las hepatitis viral por VHC
Crioglobulinemia. Tratamiento.



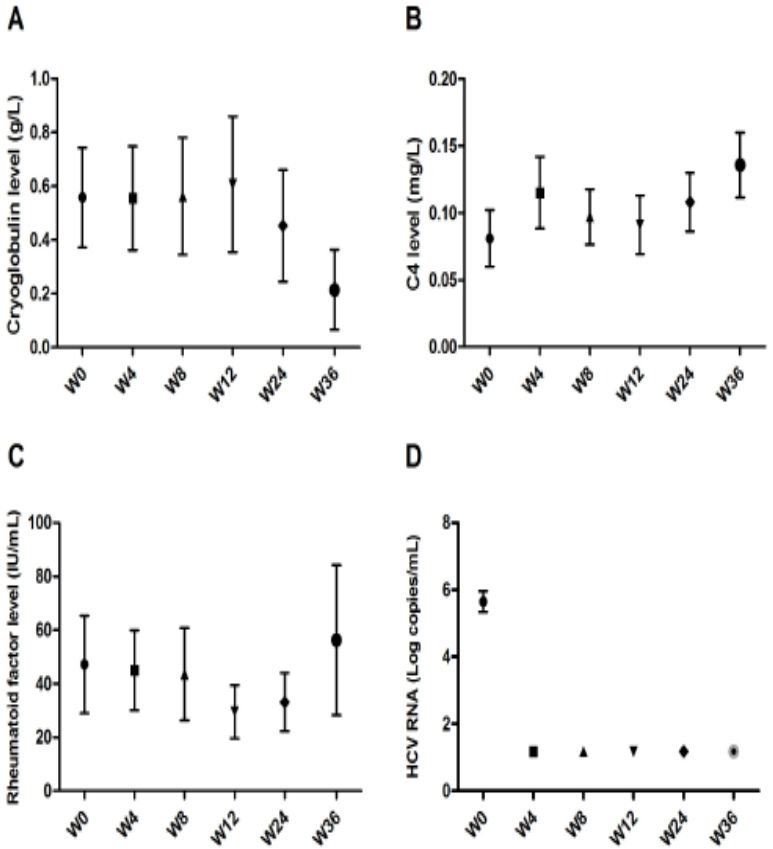
Journal of Hepatology 2017 vol. 66 | 1282–1299

Manifestaciones extrahepáticas de las hepatitis viral por VHC
Crioglobulinemia. Tratamiento.

Supplementary Figure 1: Kinetics of cryoglobulinemia (A), C4 complement level (B), rheumatoid factor activity (C), and HCV RNA (D).

Crioglobulinemia

Factor reumatoide



Please cite this article as: Saadoun D, Pol S, Ferfar Y, Alric L, Hezode C, Si Ahmed SN, de Saint Martin L, Comarmond C, Bouyer AS, Musset L, Poynard T, Resche Rigon M, Cacoub P, Efficacy and Safety of Sofosbuvir plus Daclatasvir for Treatment of HCV-associated Cryoglobulinemia Vasculitis, *Gastroenterology* (2017), doi: 10.1053/j.gastro.2017.03.006.

Manifestaciones extrahepáticas de las hepatitis viral por VHC
Crioglobulinemia. Tratamiento.

Table 1. Clinical, immunological and virological responses in HCV patients with EHMs treated with DAA-based regiments [23–54].

Patients (n)	Antiviral agent families		Clinical response			Immunological response			Virological response	
	IFN/RBV	DAAs (number of cases)	CR	PR	NR	Cryoglob. clearance	C4 levels improvement	RF reduction	SVR	Evaluation (weeks)
41	PegIFN + RBV	BCP/TLP	29/39	9/39	1/39	14/28	n.d.	n.d.	26	12–72
9	PegIFN + RBV	SOF (5), SIM + SOF (2), ASP + DCV (2)	6/7	0/7	1/7	6/7	4/5	4/5	8	24–83
50	**PegIFN-RBV**	**BCT/TLP (41), SIM (2), ASP (2), DCV (2), SOF (7)**	**35/46 (76%)**	**9/46 (20%)**	**2/46 (4%)**	**20/36 (56%)**	**4/5 (80%)**	**4/5 (80%)**	**34 (68%)**	**12–83**
48	RBV	SOF	23/30	4/30	3/30	13/29	2/3	1/3	40/47	12–36
6	RBV	SIM + SOF	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	6	24
5	RBV	LDV + SOF (3), PTP + OMT + DSB + RTN (1), DCV + SOF (1)	0/1	1/1	0/1	1/1	n.d.	n.d.	5	24
59	**RBV**	**SOF (58), PTP (1), OMT (1), DSN (1), RTN (1), SIM (6), DCV (1), LDV (3), RTN (1)**	**23/31 (74%)**	**5/31 (16%)**	**3/31 (10%)**	**14/30 (47%)**	**2/3 (67%)**	**1/3 (33%)**	**51/58 (88%)**	**12–36**
25	Free	DCV/LDV + SOF	11/15	3/15	1/15	5/14	9/12	7/8	24	4–12
18	Free	SIM + SOF	5/11	4/11	2/11	7/10	5/7	1/3	17	12–24
12	Free	PTP + OMT + DSB + RTN	10	0	2	5	5/12	6/7	12	12–24
6	Free	SIM + DCV (3), GZR + EBR (2), FDP + DLB (1)	2	1	3	3	4	3/4	6	24
61	**Free**	**DCV/LDV (28), SOF (43), SIM (21), PTP (12), OMT (12), DSB (12), RTN (12), GZB (2), EBR (2), FDB (1), DLB (1)**	**28/44 (64%)**	**8/44 (18%)**	**8/44 (18%)**	**20/42 (48%)**	**23/36 (64%)**	**17/23 (74%)**	**59 (97%)**	**4–24**

Numbers in brackets.

PegIFN, pegylated interferon alpha; RBV, ribavirin; DAAs, direct-acting agents; BCP, boceprevir; TLP, telaprevir; PTP, paritaprevir; SIM, simeprevir; OMT, ombitasvir; DCV, daclatasvir; LDV, ledipasvir; SOF, sofosbuvir; DSB, dasabuvir; RTN, ritonavir; ASP, asunaprevir; GZR, grazoprevir; EBR, elbasvir; FDP, faldaprevir; DLB, deleobuvir; CR, complete response; PR, partial response; NR, non-response; nd, not detailed; C4, complement 4; RF, rheumatoid factor; SVR, sustained virologic response.

Journal of Hepatology 2017 vol. 66 | 1282–1299

Manifestaciones extrahepáticas de las hepatitis viral por VHC

Crioglobulinemia. Tratamiento.

Table 1. Direct-Acting Antiviral (DAA) Therapy and HCV-Related Cryoglobulinemic Vasculitis (CryoVas), According to Study and Year.*

Variable	Saadoun et al.,[14] 2016	Sise et al.,[15] 2016	Gragnani et al.,[16] 2016	Cacoub et al.,[17] 2017	Emery et al.,[18] 2017	Comarmond et al.,[19] 2017	Saadoun et al.,[20] 2017	Lauletta et al.,[21] 2017	Bonacci et al.,[22] 2018	Cacoub et al.,[23] 2019†
Study design	Open-label trial	Case series	Prospective cohort	Retrospective cohort	Retrospective cohort	Open-label trial	Open-label trial, prospective cohort	Prospective cohort	Prospective cohort	Prospective cohort
No. of patients	24	12	44	27‡	18§	27	41	22	46¶	148
Cirrhosis — no. (%)	12 (50)	6 (50)	17 (39)	NA	18 (100)	11 (41)	18 (44)	12 (55)	26 (57)	70 (54)
Liver fibrosis score — no. (%)‖	F0–F2: 10 (42) F3–F4: 14 (58)	NA	F0–F2: 23 (52) F3–F4: 21 (48)	F0–F2: 17 (63) F3–F4: 10 (37)	NA	F0–F2: 10 (37) F3–F4: 17 (63)	F0–F2: 15 (37) F3–F4: 26 (63)	F0–F2: 10 (45) F3–F4: 12 (55)	F0–F2: 18 (39) F3–F4: 28 (61)	F0–F2: 59 (46) F3–F4: 70 (54)
CryoVas symptoms before DAA — no. (%)	Purpura: 16 (67) Arthralgia: 14 (58) Peripheral neuropathy: 16 (67) Renal involvement: 5 (21)	Purpura: 6 (50) Arthralgia: 7 (58) Peripheral neuropathy: 4 (33) Renal involvement: 6 (50)	Purpura: 32 (73) Arthralgia: 26 (59) Peripheral neuropathy: 28 (64) Renal involvement: 4 (9)	Purpura: 16 (59) Arthralgia: 9 (33) Peripheral neuropathy: 16 (59) Renal involvement: 7 (26)	Purpura: 15 (83) Arthralgia: 3 (17) Peripheral neuropathy: 6 (33) Renal involvement: 10 (56)	Purpura: 24 (89) Arthralgia: NA Peripheral neuropathy: 13 (48) Renal involvement: 7 (26)	Purpura: 31 (76) Arthralgia: 26 (63) Peripheral neuropathy: 21 (51) Renal involvement: 5 (12)	Purpura: 22 (100) Arthralgia: 22 (100) Peripheral neuropathy: 2 (9) Renal involvement: 4 (18)	Purpura: 29 (63) Arthralgia: 16 (35) Peripheral neuropathy: 19 (41) Renal involvement: 9 (20)	Purpura: 85 (57) Arthralgia: 94 (64) Peripheral neuropathy: 86 (58) Renal involvement: 25 (17)
SVR after DAA — %	74	83	100	75	89	82	100	100	100	97
Concomitant immunosuppression — no.	7 (RTX, PLEX, GC)	6 (RTX, PLEX)	2 (RTX)	9 (RTX), 6 (PLEX), 6 (RTX, PLEX)	4 (RTX, PLEX)	NA	2 (RTX, PLEX)	NA	3 (RTX, PLEX)	21 (GC, IS, or PLEX)
Complete clinical response — no. (%)	21 (88)	5 (42)	29 (66)	15 (56)	7 (39)	24 (89)	37 (90)	14 (64)	37 (80)	106 (72)
Partial clinical response — no. (%)	3 (12)	5 (42)	12 (27)	11 (41)	4 (22)	0	4 (10)	5 (23)	5 (11)	33 (22)
No clinical response — no. (%)	0	2 (17)	3 (7)	1 (4)	7 (39)	3 (11)	0	3 (14)	4 (9)	7 (5)
BVAS score**	NA	NA	Baseline: 5.4±3.5; last visit: 2.3±2.2††	NA	NA	NA	Baseline: 8 (4–17); last visit: 0 (0–5)††	NA	Baseline: 7; last visit: 0††	NA
Cryoglobulin clearance — %	46	44	40	63	29	37	50	48	66	53
Deaths — no. (%)	2 (8)	0	0	4 (15)	0	0	0	0	0	4 (3)
Follow-up — mo	6	6	10.5	18	6	6–9	9	9–12	24	15.3
Limitations	Lack of control group; included both previously untreated and previously treated patients	Small sample (mainly for renal involvement), lack of control group	Lack of control group	Single center, retrospective design, lack of control group	Retrospective design, small sample, lack of control group, short follow-up	Lack of control group, short follow-up	Lack of control group	Small sample, lack of control group	Single center, lack of control group	Lack of control group

* GC denotes glucocorticoid, IS immunosuppressant, NA not available, PLEX plasmapheresis, RTX rituximab, and SVR sustained virologic response.
† For cirrhosis and for the liver fibrosis score, the percentages are based on 129 patients.
‡ Eleven patients (41%) were treated with interferon-containing regimens.
§ Seven patients (39%) were treated with interferon-containing regimens.
¶ Seven patients (15%) were treated with interferon-containing regimens along with DAA.
‖ The fibrosis score ranges from F0 (no fibrosis) to F4 (cirrhosis).
** The Birmingham Vasculitis Activity Score (BVAS, version 3) ranges from 0 to 63, with higher scores indicating greater disease activity. Plus–minus values are means ±SD. Numbers in parentheses are ranges.
†† The difference was significant.

N Engl J Med 2021;384:1038-52.
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Manifestaciones extrahepáticas de la hepatitis C
Diagnóstico diferencial enfermedades reumáticas primarias

	Mixed cryogl. HCV+	Sicca syndrome HCV+	pSjögren's syndrome	Arthritis HCV+	Rheumatoid arthritis
Symptoms					
Purpura	+++	+/-	+/-	+/-	+/-
Weakness	+++	+	+	+	+/-
Arthralgias	+++	+/-	+/-	+++	+++
Oligoarthritis	+	+	+	+	+
Polyarthritis	+/-	+/-	+	+	+++
Erosive arthritis	-	-	+/-	+/-	+++
sicca syndrome	+	+++	+++	+/-	+/-
Renal inv.	++	+/-	+	+/-	+/-
Peripheral neuropathy	++	+/-	+	+/-	+/-
B-NHL	+	+/-	+	+/-	+/-

https://www.sciencedirect.com/science/article/abs/pii/S1568997216302014?via%3Dihub

Manifestaciones extrahepáticas de la hepatitis C
Diagnóstico diferencial enfermedades reumáticas primarias

	Mixed cryogl. HCV+	Sicca syndrome HCV+	pSjögren's syndrome	Arthritis HCV+	Rheumatoid arthritis
Laboratory alterations					
Mixed cryoglobulins	+++	+/-	+	+/-	+/-
Low complement C4	+++	+/-	-	+/-	-
RF	+++	+/-	+++	+/-	++
anti-CCP Ab	-	-	-	-	++
ANA	+/-	+/-	+++	+/-	+/-
anti-SSA/SSB Ab	+/-	+/-	+++	-	-
Salivary gland biopsy	+/-	+/-	+++	+/-	+/-

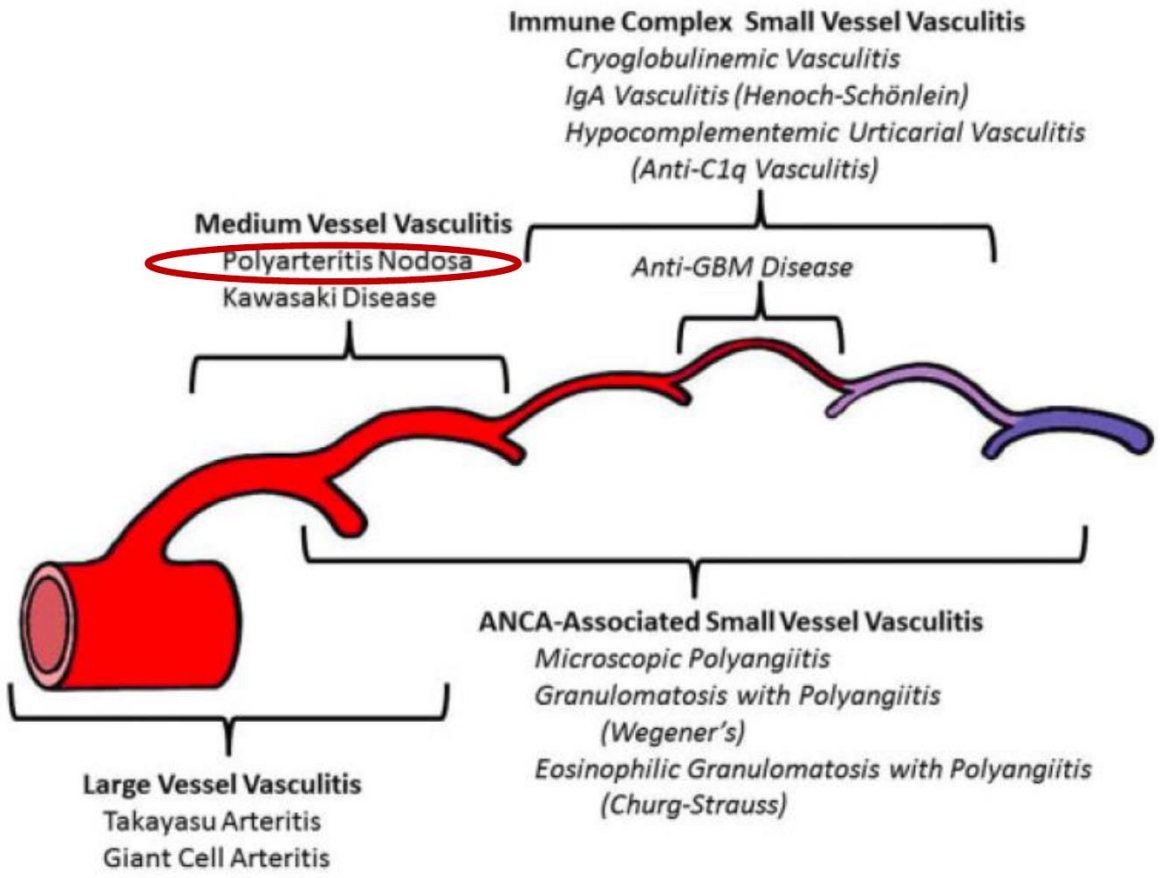
Colored areas highlight the parameters useful for differential diagnosis.

B-NHL: B-cell non-Hodgkin's lymphomas; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide antibodies; ANA: anti-nuclear antibodies

https://www.sciencedirect.com/science/article/abs/pii/S1568997216302014?via%3Dihub

Manifestaciones extrahepáticas de la hepatitis B

PAN



Vasculitis	Definición
Vasculitis de Vaso de mediano tamaño	
Poliarteritis nodosa (PAN)	Arteritis necrotizante de arterias de pequeño y mediano calibre sin GN o vasculitis en arteriolas, capilares o vénulas. No se asocia a ANCAs
Vasculitis de vaso de pequeño tamaño	
Vasculits ANCAs positivas	
Poliangeítis microscópica (PAM)	Vasculitis necrotizante con pocos o sin depósitos inmunes afectando a vasos de pequeño tamaño (capilares, vénulas o arteriolas). Puede existir arteritis necrotizante afectando arterias de pequeño y mediano tamaño. Es muy frecuente la GNM necrotizante. Puede existir la capilaritis pulmonar. No hay granulomas

Jennette et al. Artritis Rheum 2013:65:1

Jennette JC et al. Arthritis Rheum. 2013;65:1-11

Manifestaciones extrahepáticas de la hepatitis B
PAN

PAN clásica

Forma **sistémica**

Formas **localizadas** (piel, vesícula biliar, apéndice)

Vasculitis tipo PAN/ asociadas a etiología conocida

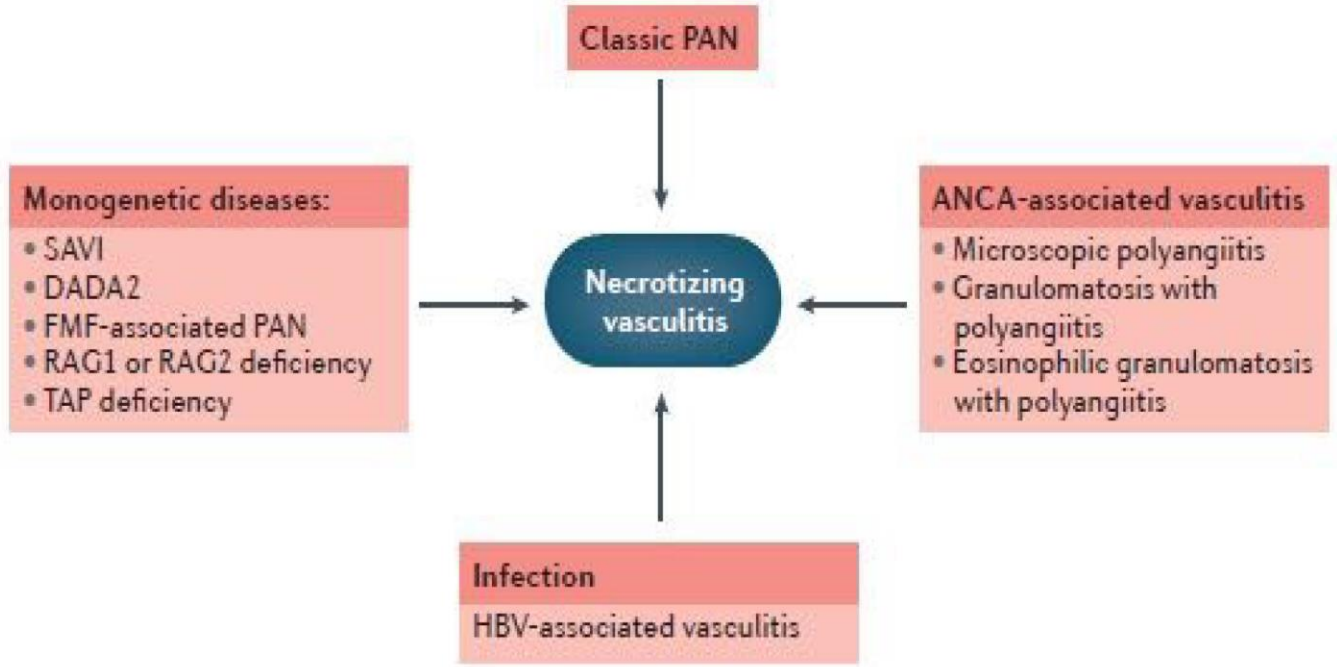
Asociada a **infecciones**

- VHB, VHC
- HIV, parvovirus
- Estreptococo
- Varicela zoster

Asociada a **conectivopatías:** AR, LES, SS

Leucemia de células peludas

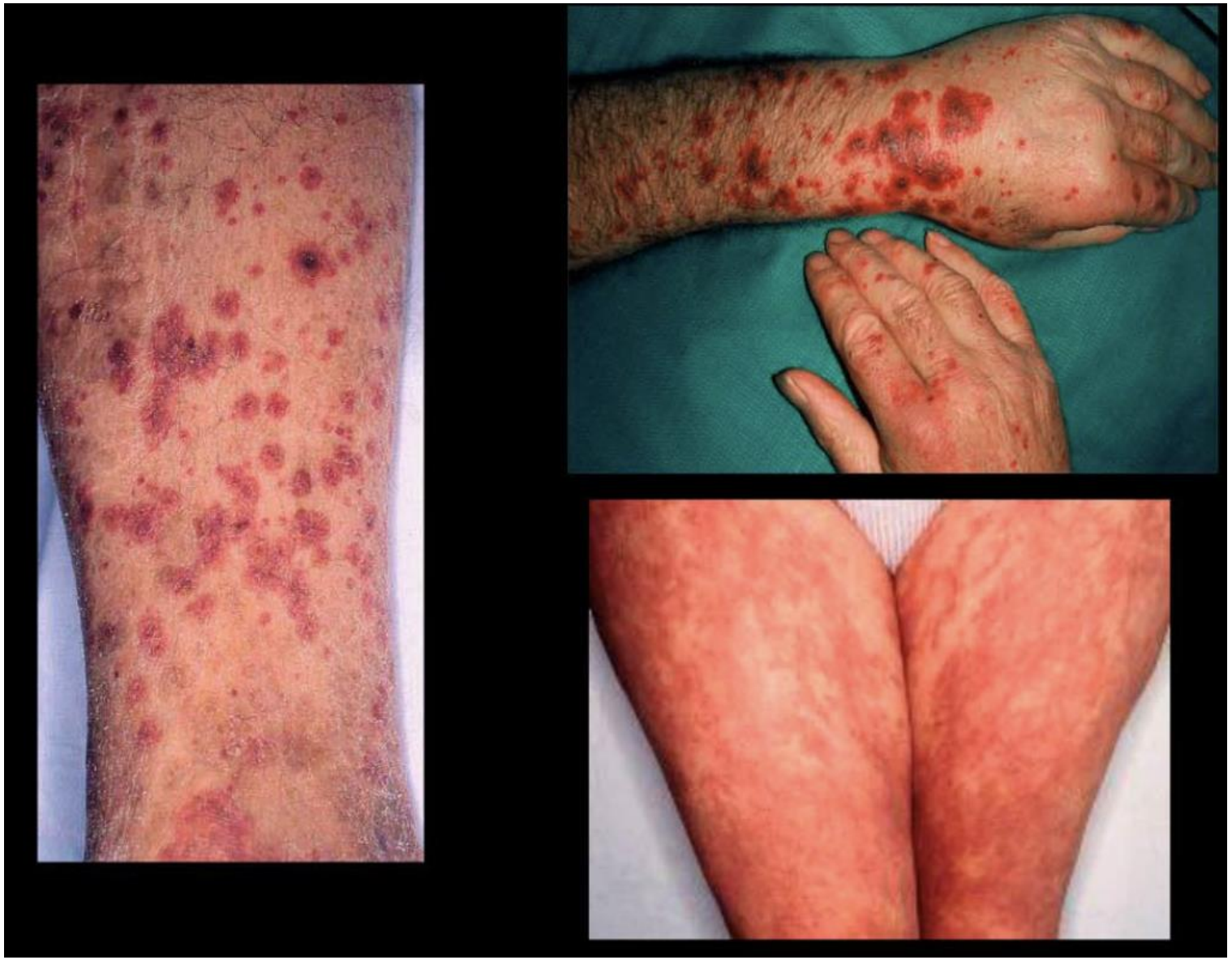
Asociada a déficit de adenosin deaminasa 2 (DADA2)
Asociada a Fiebre mediterránea familiar (FMF)



Nature Reviews Reumatology. Vol 13 .June 2017

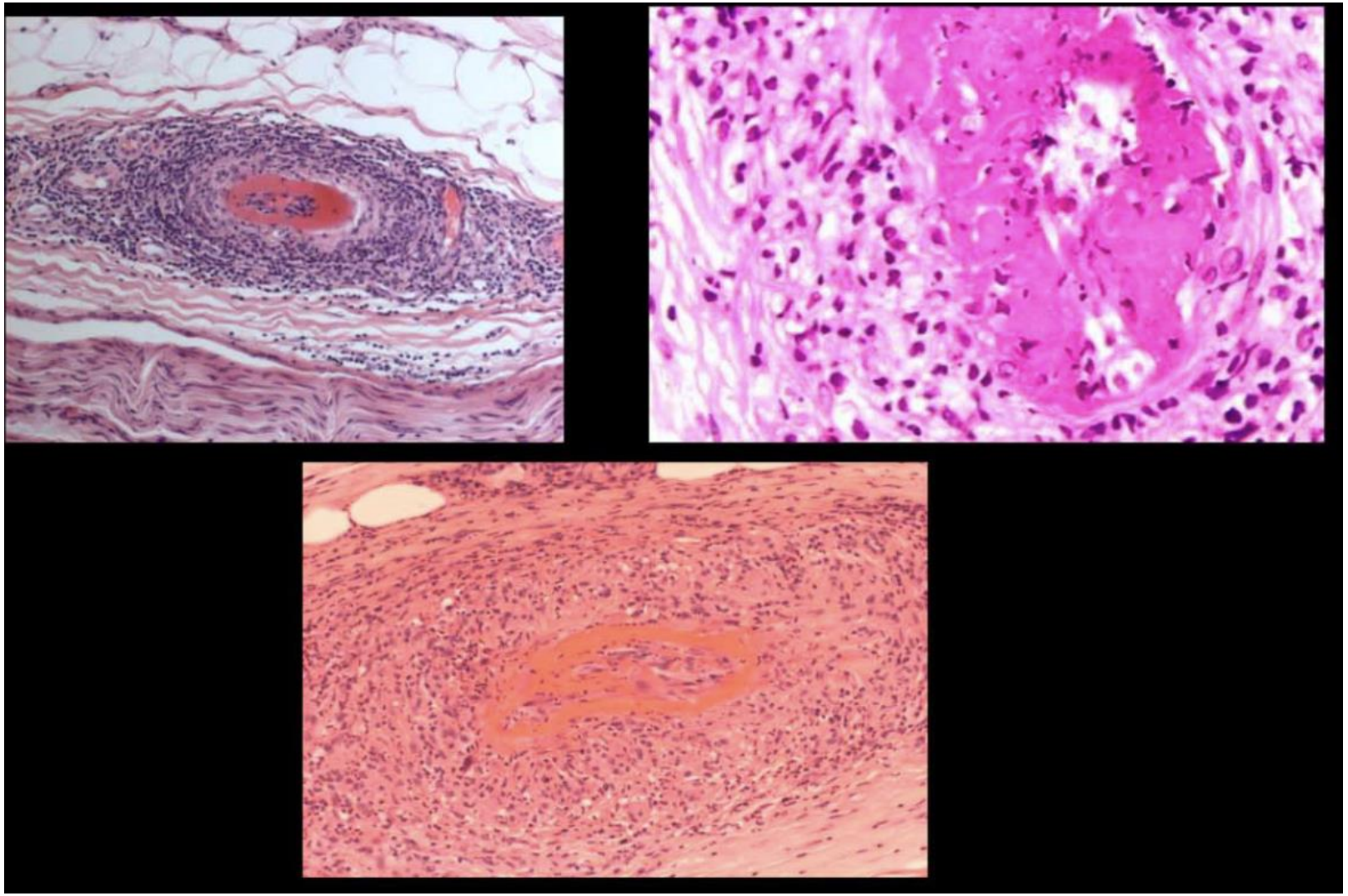
Manifestaciones extrahepáticas de la hepatitis B

Vasculitis cutánea y lívido



Am J Gastroenterol 2022;117:253–263. https://doi.org/10.14309/ajg.0000000000001575

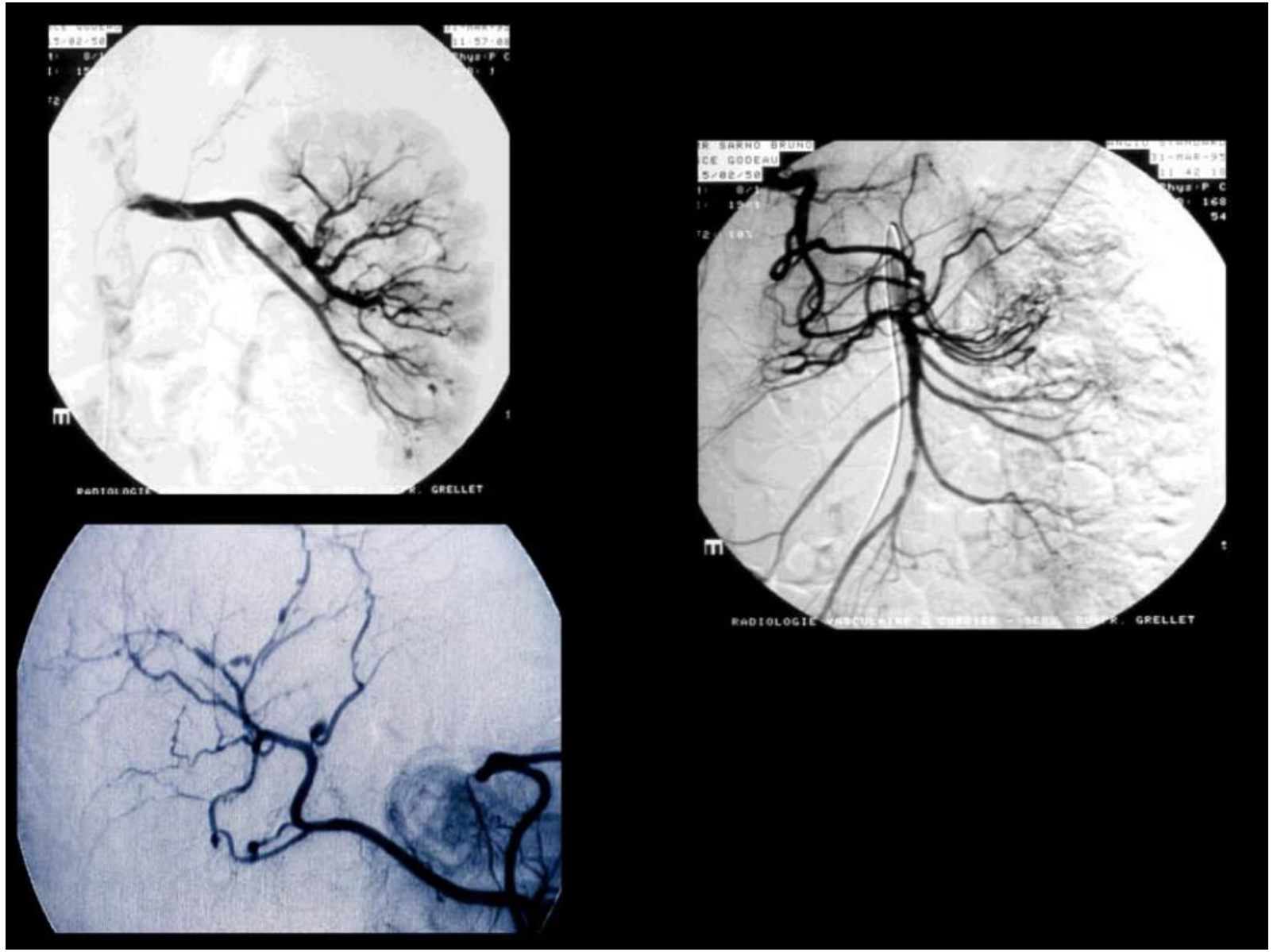
Manifestaciones extrahepáticas de la hepatitis B
Vasculitis necrotizante nervio periférico



Am J Gastroenterol
2022;117:253–263.
https://doi.org/10.14309/
ajg.0000000000001575

Manifestaciones extrahepáticas de la hepatitis B

Micro-aneurismas y estenosis



Am J Gastroenterol
2022;117:253–263.
https://doi.org/10.14309/
ajg.0000000000001575

Manifestaciones extrahepáticas de la hepatitis B
PAN

PAN-HB

PAN asociada a VHB:
Inmunocomplejos

Frecuencia ha disminuido
de 30% de pcts con PAN al 5% : vacunas y seguridad transfusional

Hepatitis B Virus-Associated Polyarteritis Nodosa
Clinical Characteristics, Outcome, and Impact of Treatment in 115 Patients

*Loïc Guillevin, MD, Alfred Mahr, MD, Patrice Callard, MD, Pascal Godmer, MD, Christian Pagnoux, MD, Emmanuelle Leray, MD, and Pascal Cohen, MD, for the French Vasculitis Study Group**

No. of PAN	Period 1972–1979								Period 1980–1989										Period 1990–2002												Total
HBV	2	0	1	1	1	4	3	1	2	3	5	7	6	6	17	8	6	4	1	2	8	2	6	2	2	0	1	6	3	3	2	**115**
Non-HBV	0	2	2	2	2	2	3	1	1	5	9	9	8	9	8	8	9	14	17	8	7	7	7	7	8	18	11	15	7	7	13	**226**

TABLE 1. Frequency of Hepatitis B Virus-Associated Polyarteritis Nodosa Cases Among Polyarteritis Nodosa Cases According to Time of Occurrence

5-Year Period	No. of HBV-PAN Cases/ Total No. of PAN Cases	%
1972–1976	5/13	38.5
1977–1981	13/25	52.0
1982–1986	41/84	48.8
1987–1991	21/77	27.3
1992–1996	20/56	35.7
1997–2002*	15/86	17.4

*This final period lasted 6 years.

PAN: manifestación extra-hepática mas grave de la HB. Al cabo de seis meses.

Se observa una reducción en la incidencia tras la implementación de la vacunación

Tratar la infección y la vasculitis

Guillevin et al. Medicine 2005; 84:313.

Manifestaciones extrahepáticas de la hepatitis B
PAN relacionada con el VHB

Table 1. Main characteristics of patients with primary vs HBV-related polyarteritis nodosa (*Pagnoux C et al, 2010* [ref. 40])

Features	Primary PAN	HBV-related PAN	*P* value
Number of patients	225	123	
Time to onset, mean ± SD, mo	8.9 ± 27.3	4.7 ± 12.4	0.05
Weight loss, mean ± SD, kg	5.4 ± 5.9	7.9 ± 7.2	0.001
Neuropathy, %	64.4	82.1	<0.0001
Recent onset hypertension, %	27.1	48.8	<0.0001
Severe hypertension, %	4.9	10.6	0.05
Orchitis, %	13.1	24.1	0.02
Skin involvement, %	57.8	35.0	<0.0001
Gut involvement, %	30.1	50.4	<0.0001
Cardiac involvement, %	4.4	13.0	0.004
FFS ≥ 1, %	33.3	52.9	0.002
BVAS mean ± SD	15.1 ± 7.6	19.1 ± 9.1	<0.0001
Microaneurysms/stenoses, %	49	71.2	0.006

BVAS, Birmingham Vasculitis Activity Score; FFS, Five-Factor Score; HBV, hepatitis B virus; PAN, polyarteritis nodosa.

Am J Gastroenterol 2022;117:253–263. https://doi.org/10.14309/ajg.0000000000001575

Manifestaciones extrahepáticas de la hepatitis B
PAN relacionada con el VHB

Table 4. Efficacy of antiviral therapy in hepatitis B virus-related extrahepatic manifestations

Extrahepatic manifestations	Treatment	No. of patients	Extrahepatic Improvements	Reference, author, yr
Polyarteritis nodosa	Corticosteroids + LAM + plasma exchanges	10	90% (9/10)	Guillevin et al. 2004 (ref 45)
Mixed cryoglobulinemia vasculitis	Steroids (8), NA (ETV:5, ADV:1, LAM:1, IFN:2)	17	No disease progression	Mazzaro et al. 2016 (ref 52)
MPGN	Steroids + NA (LAM, ETV, ADV)	317	Reduction of proteinuria by 4 fold	Zheng et al. 2012 (ref 11)
PRO	NA (LAM, ADV, TDF, ETV, TBV)	242	Reduction of viral load associated with increase PROs	Younossi et al. 2018 (ref 105)

ADV, adefovir; ETV, entecavir; HBsAg, hepatitis B surface antigen; LAM, lamivudine; MPGN, membranoproliferative glomerulonephritis; N/A, not applicable; PEG-IFN, pegylated interferon; PRO, patient-reported outcome; TAF, tenofovir alafenamide; TBV, telbivudine; TDF, tenofovir disoproxil fumarate.

Am J Gastroenterol 2022;117:253–263. https://doi.org/10.14309/ajg.0000000000001575

Manifestaciones extrahepáticas de las hepatitis viral por VHC
LNH.

- El riesgo general de que se desarrolle un linfoma de células B en pacientes que tienen una infección crónica por el VHC con crioglobulinemia es aproximadamente 35 veces mayor que el riesgo de la población general, o 12 veces más si se excluyen los linfomas no agresivos.
- Los linfomas B-NHL suelen desarrollarse tras un largo periodo de infección por el VHC (>15 años).

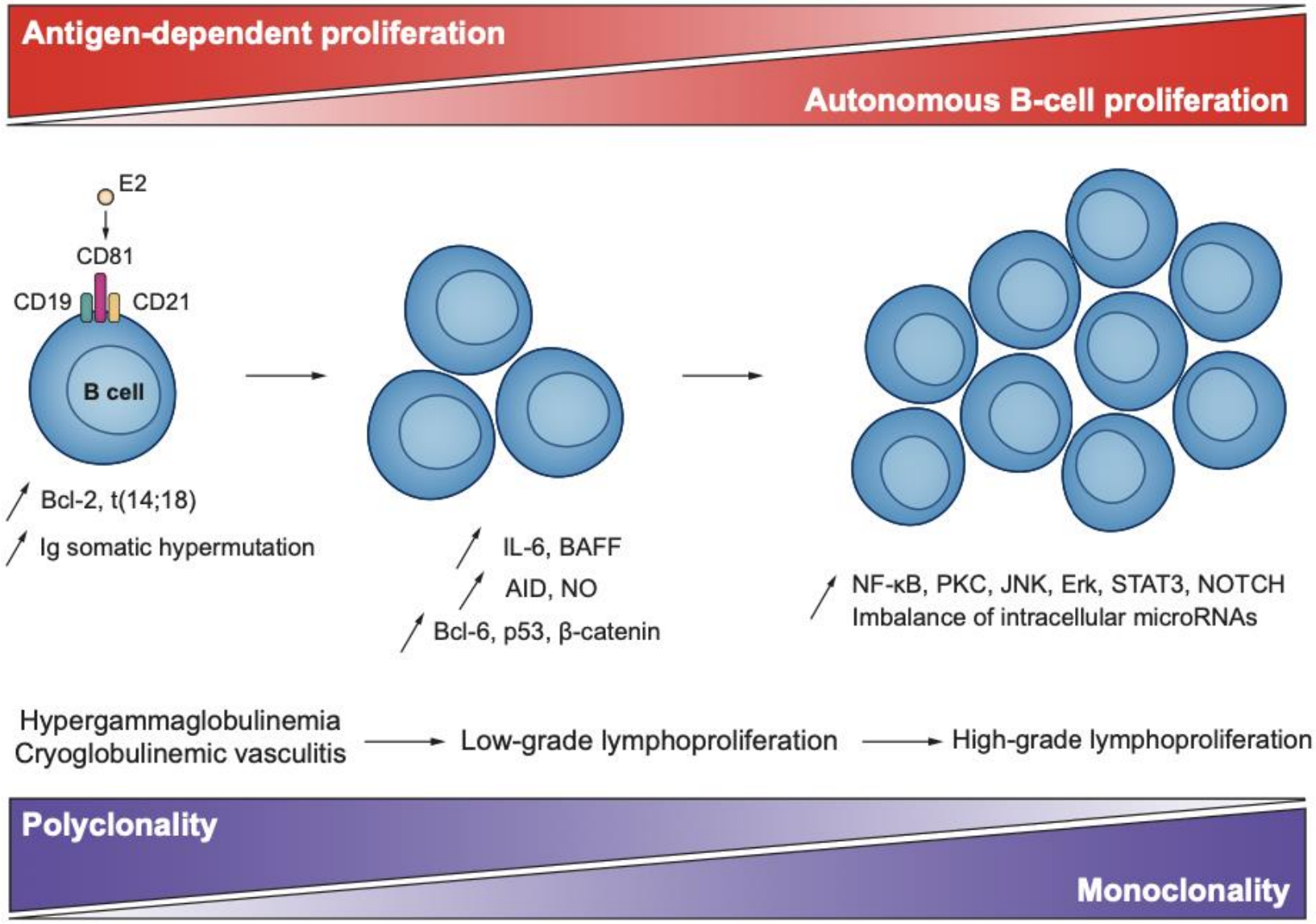
- Factores de riesgo de linfoma en pacientes con VHC:
  - Niveles séricos de niveles de crioglobulina superiores a 0,6 g por litro,
  - Existencia de vasculitis crioglobulinémica mixta
  - Hipogammaglobulinemia

La evolución del LNH-B se produce independientemente de la progresión de la fibrosis hepática (Tabla 2).

	N= 1255
Diagnóstico LNH	59
No agresivo	31
Agresivo	20
MALT	6
No clasificado	2

Monti G et al. Arch Intern Med 2005

Manifestaciones extrahepáticas de las hepatitis viral por VHC
LNH.

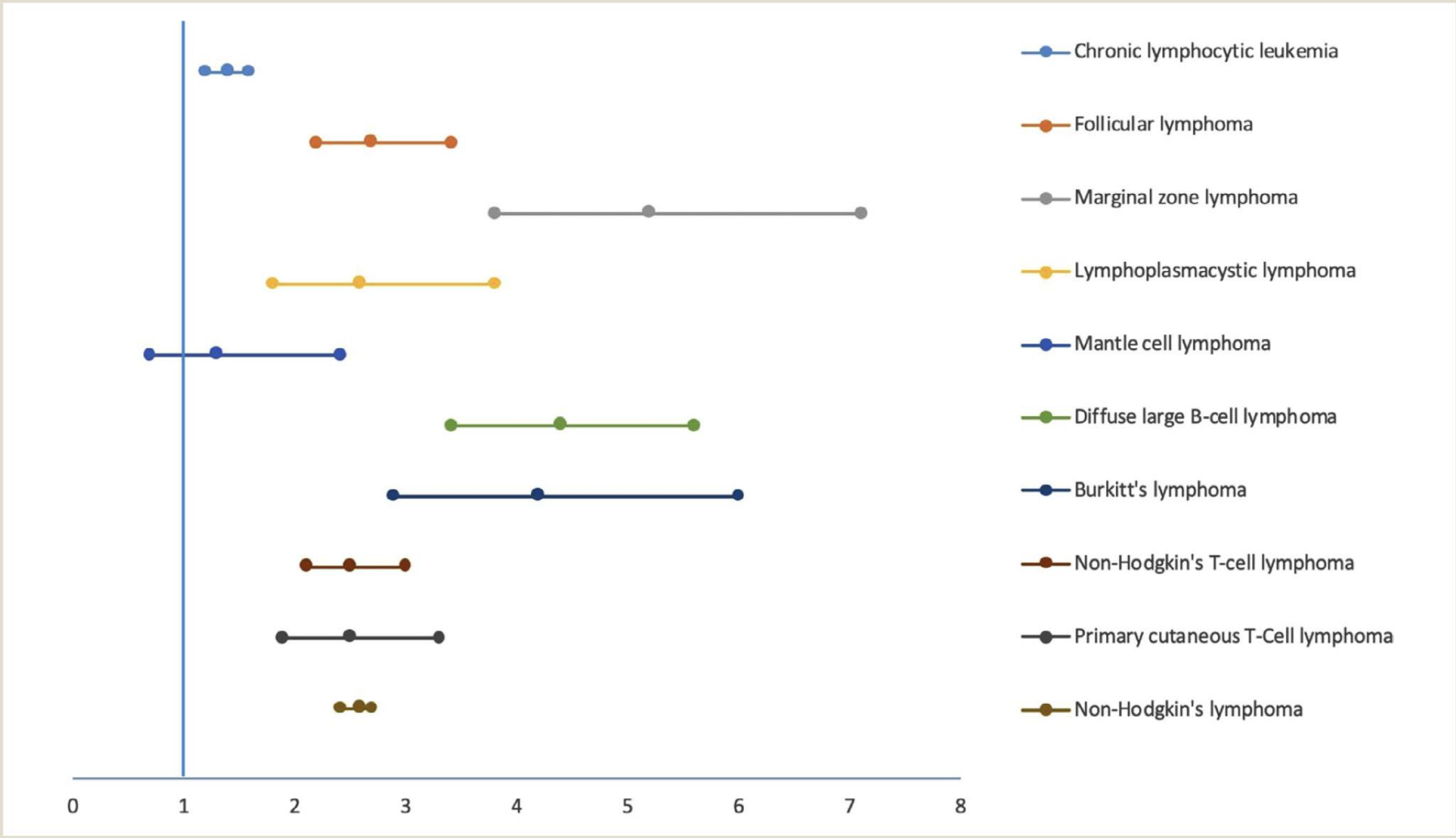


Cacoub P, Comarmond C, Vieira M, Régnier P, Saadoun D. HCV-related lymphoproliferative disorders in the direct-acting antiviral era: From mixed cryoglobulinaemia to B-cell lymphoma. J Hepatol. 2022 Jan;76(1):174-185. doi: 10.1016/j.jhep.2021.09.023. Epub 2021 Sep 29. PMID: 34600000.

Manifestaciones extrahepáticas de las hepatitis viral por VHC

LNH.

Figure 1 Relative risk of NHL in HCV infected compared to HCV negative population. Filled circle is the relative risk, and line through the circle is the 95% confidence interval.



Alkrekshi A, Kassem A, Park C, Tse W. Risk of Non-Hodgkin's Lymphoma in HCV Patients in the United States Between 2013 and 2020: A Population-Based Study. Clin Lymphoma Myeloma Leuk. 2021 Nov;21(11):e832-e838. doi: 10.1016/j.clml.2021.06.014. Epub 2021 Jun 24. PMID: 34330674.

Manifestaciones extrahepáticas de las hepatitis viral por VHC

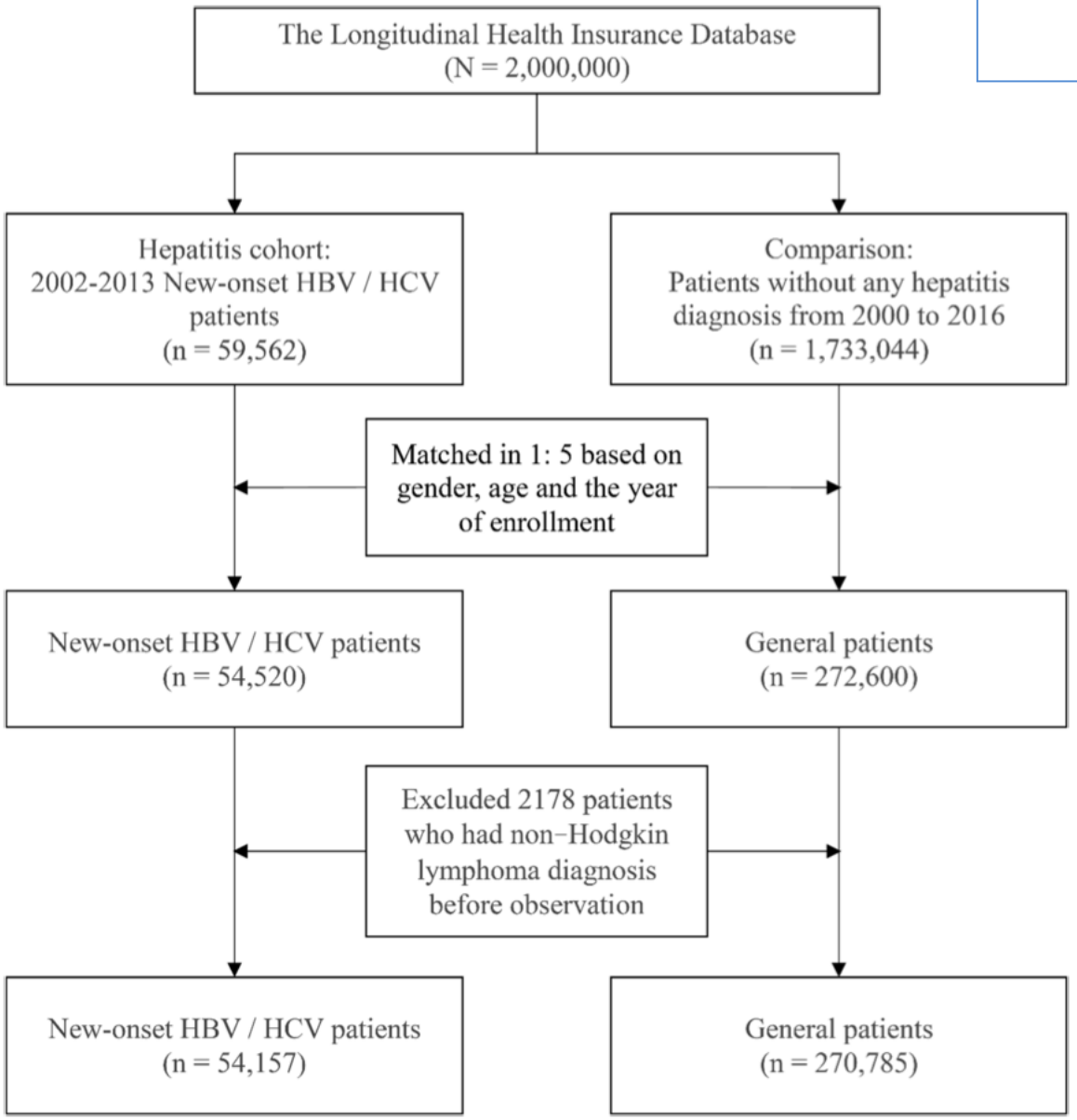
LNH.

	HCV Population	Control Population	Odds Ratios (Confidence Interval 95%),
	N = 129,970	*N* = 37,961,970	*P* Value
Chronic lymphocytic leukemia	220	45,370	1.4 (1.2-1.6), $P < .001$
Follicular lymphoma	80	8620	2.7 (2.2-3.4), $P < .001$
Marginal zone lymphoma	40	2240	5.2 (3.8-7.1), $P < .001$
Lymphoplasmacystic lymphoma	30	3330	2.6 (1.8-3.8), $P < .001$
Diffuse large B-cell lymphoma	60	4010	4.4 (3.4-5.6), $P < .001$
Burkitt's lymphoma	30	2100	4.2 (2.9-6.0), $P < .001$
Mantle cell lymphoma	10	2240	1.3 (0.7-2.4), $P = .402$
Non-Hodgkin's T-cell lymphoma	120	14,100	2.5 (2.1-3.0), $P < .001$
Primary cutaneous T-cell lymphoma	50	5930	2.5 (1.9-3.3), $P < .001$
Non-Hodgkin's lymphoma[a]	940	107,480	2.6 (2.4-2.7), $P < .001$

[a] Total cases of NHL exceed the sum total of subtypes listed as it is more inclusive and contains patient without a specified subtype.

Alkrekshi A, Kassem A, Park C, Tse W. Risk of Non-Hodgkin's Lymphoma in HCV Patients in the United States Between 2013 and 2020: A Population-Based Study. Clin Lymphoma Myeloma Leuk. 2021 Nov;21(11):e832-e838. doi: 10.1016/j.clml.2021.06.014. Epub 2021 Jun 24. PMID: 34330674.

Manifestaciones extrahepáticas de las hepatitis viral por VHC. LNH.



5. Conclusions

HBV and HCV infections play a significant role in the development of NHL. In patients with HBV and patients with HCV, both receiving antiviral agents, chronic coinfection with HBV and HCV was associated with an increased risk of NHL in a Taiwanese population. In addition, the relative risk of developing NHL increases with increasing age and some comorbidities (such as HPL, CKD, SLE, HIV, and organ transplant).

Lai, Y.-R.; Chang, Y.-L.; Lee, C.-H.; Tsai, T.-H.; Huang, K.-H.; Lee, C.-Y. Risk of Non-Hodgkin Lymphoma among Patients with Hepatitis B Virus and Hepatitis C Virus in Taiwan: A Nationwide Cohort Study. *Cancers* **2022**, *14*, 583. https://doi.org/10.3390/ cancers14030583

Manifestaciones extrahepáticas de las hepatitis viral por VHC
LNH. Respuesta al tratamiento antiviral.

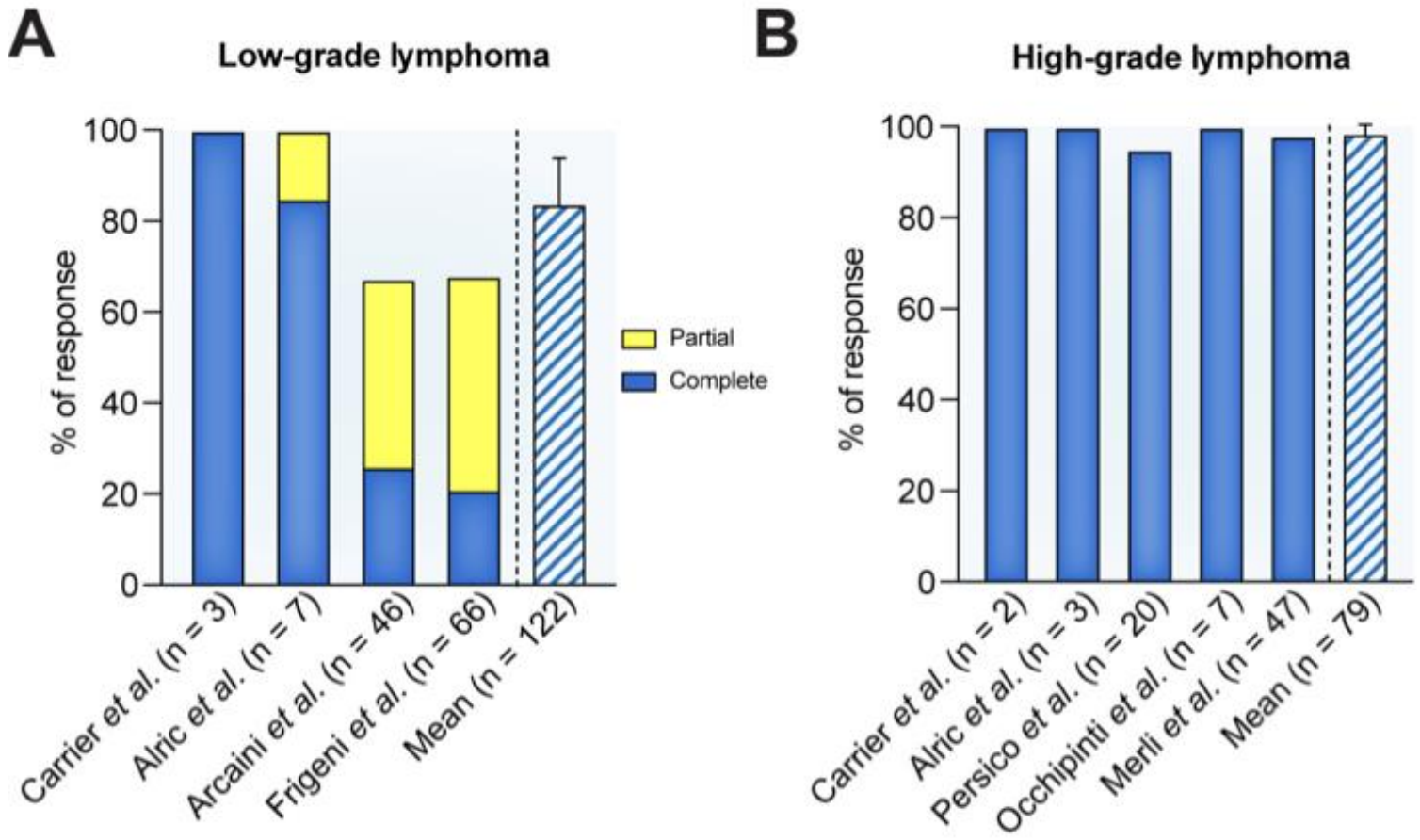


Fig. 6. Haematological response of B-cell non-Hodgkin lymphoma to direct-acting antiviral therapy. Pooled response rates with estimated means obtained from studies evaluating the haematological response of B-cell non-Hodgkin lymphoma to HCV-targeting direct-acting antivirals. (A) Partial and complete responses of low-grade B-cell non-Hodgkin lymphoma. (B) Overall responses of high-grade B-cell non-Hodgkin lymphoma.

Cacoub P, Comarmond C, Vieira M, Régnier P, Saadoun D. HCV-related lymphoproliferative disorders in the direct-acting antiviral era: From mixed cryoglobulinaemia to B-cell lymphoma. J Hepatol. 2022 Jan;76(1):174-185. doi: 10.1016/j.jhep.2021.09.023. Epub 2021 Sep 29. PMID: 34600000.

Manifestaciones extrahepáticas de la hepatitis C
LNH. Respuesta al tto antiviral.

Table 2. DAA Therapy and B-Cell Non-Hodgkin's Lymphoma (NHL) in HCV-Infected Patients, According to Study and Year.

Variable	Carrier et al.,[29] 2015	Alric et al.,[30] 2016	Arcaini et al.,[31] 2016	Persico et al.,[32] 2018	Occhipinti et al.,[33] 2019	Merli et al.,[34] 2019	Frigeni et al.,[35] 2020
Study design	Case series	Prospective cohort	Retrospective cohort	Prospective cohort	Case series	Retrospective cohort	Retrospective cohort
No. of patients	5	10	46	20	7	47	66
Cirrhosis — no. (%)	1 (20)	1 (10)	7 (15)	4 (20)	1 (14)	12 (26)	7 (11)
Liver fibrosis score — no. (%)	F0–F2: 4 (80) F3–F4: 1 (20)	F0–F2: 3 (30) F3–F4: 7 (70)	NA	F0–F2: 14 (70) F3–F4: 6 (30)	NA	F0–F2: 28 (60) F3–F4: 19 (40)	NA
Lymphoma subtype — no. (%)*	MZL: 3 (60) DLBCL: 2 (40)	MZL: 6 (60) DLBCL: 3 (30) Other: 1 (10)	MZL: 37 (80) LPL: 2 (4) FL: 2 (4) CLL/SLL: 4 (9) NHL NOS: 1 (2)	DLBCL	DLBCL	DLBCL: 45 (96) FL: 2 (4)	MZL: 53 (80) Other: 13 (20)
SVR — %	100	90	98	100	100	96	98
Chemotherapy — no. (%)	Concomitant: 3 (60)	Concomitant: 9 (90)	No	Concomitant: 20 (100)	Before DAA: 2 (29) Concomitant: 5 (71)	Before DAA: 38 (81) Concomitant: 9 (19)	No
Complete hematologic response — no. (%)	5 (100)	9 (90)	12 (26)	19 (95)	7 (100)	46 (98)	14 (21)
Partial hematologic response — no. (%)	0	1 (10)	19 (41)	0	0	0	31 (47)
Stable hematologic disease — no. (%)	0	0	11 (24)	0	0	0	15 (23)
Progression or no response — no. (%)	0	0	4 (9)	1 (5)	0	1 (2)	5 (8)
1-Year progression-free survival — %	100	100	75	95	100	93.1†	79‡
Complete response stratified by liver fibrosis score — no. (%)	F0–F2: 4 (100) F3–4: 1 (100)	F0–F2: 3 (100) F3–4: 6 (86)	NA	NA	NA	NA	NA
Follow-up — mo	9–12	12	8	12	12	33.6	17
Limitations	Retrospective design, small sample, short follow-up	Small sample, short follow-up	Retrospective design, heterogeneous DAA regimens and timing, possible selection bias, short follow-up	Small sample, short follow-up	Retrospective design, small sample, short follow-up	Retrospective design, selection bias, heterogeneous DAA regimens and timing after chemotherapy	Retrospective design, absence of centralized histologic diagnosis, possible selection bias

* CLL/SLL denotes chronic lymphocytic leukemia or small lymphocytic lymphoma, DLBCL diffuse large B-cell lymphoma, FL follicular lymphoma, LPL lymphoplasmacytic lymphoma, MZL marginal-zone lymphoma, and NOS not otherwise specified.
† Progression-free survival at 2 years is shown.
‡ Estimated progression-free survival at 3 years is shown.

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Direct-Acting Antivirals as Primary Treatment for Hepatitis C Virus–Associated Indolent Non-Hodgkin Lymphomas: The BArT Study of the Fondazione Italiana Linfomi

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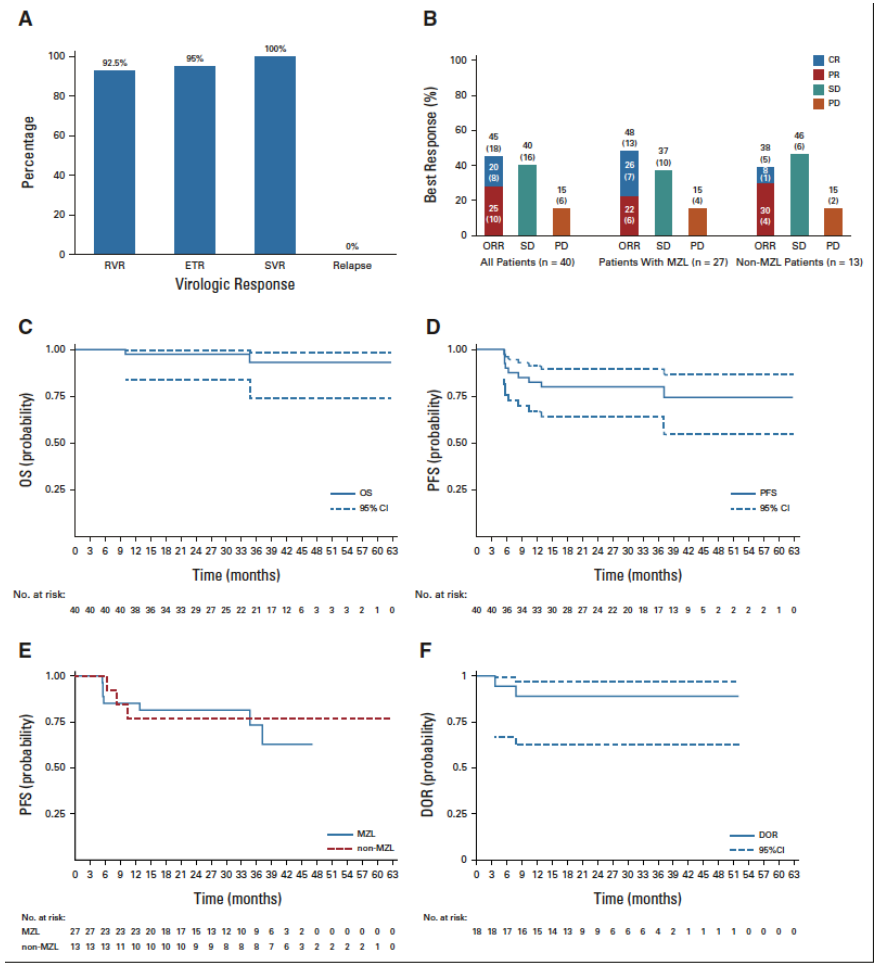


Manifestaciones extrahepáticas de las hepatitis viral por VHC

LNH.

CONTEXT

Key Objective

The most convincing evidence supporting the etiologic role of hepatitis C virus (HCV) in indolent non-Hodgkin lymphomas was represented by retrospective observations of lymphoma regression after viral eradication by interferon-free direct-acting antivirals (DAAs). To our knowledge, the phase II BArT trial is the first prospective study evaluating genotype-appropriate DAAs as primary treatment in patients with HCV-associated indolent non-Hodgkin lymphomas not requiring immediate conventional therapy, with the aim to assess both virologic and lymphoma responses.

Knowledge Generated

We demonstrated that (1) all patients enrolled achieved sustained virologic response, with negligible toxicity, (2) nearly half of the patients attained an objective response, without differences between marginal zone lymphoma and non–marginal zone lymphoma subtypes, and (3) responses were highly durable.

Relevance (*J.W. Friedberg*)

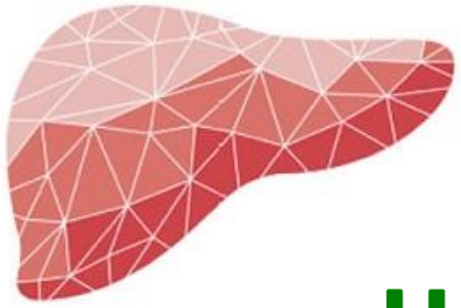
The results of BArT study suggest eradication of HCV with DAAs may result in durable lymphoma regression in a subset of patients. Further studies in patients with HCV-related indolent lymphomas not requiring immediate conventional treatment from other geographic areas are warranted.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.

Manifestaciones extrahepáticas de las hepatitis viral por VHC
LNH. Puntos clave.

- La infección crónica por el VHC es una enfermedad sistémica que provoca manifestaciones hepáticas y extrahepáticas
- El linfoma no Hodgkin (LNH) de células B está asociado a la infección por el VHC (riesgo relativo de ~1,5) y está relacionado con la estimulación antigénica crónica y, en menor medida, con la transformación directa asociada a la presencia del virus
- Las terapias antivirales permiten una respuesta virológica y hematológica sostenida en dos tercios de los pacientes con LNH relacionado con el VHC
- El VHC también infecta a las células extrahepáticas y podría inducir alteraciones cualitativas y cuantitativas crónicas del repertorio inmunitario y del microambiente tisular local, lo que podría inducir diversos cánceres no hepáticos
- En general, se acepta que la infección crónica por el VHC aumenta el riesgo de LNH y de colangiocarcinoma intrahepático.

MÁSTER EN HEPATOLOGÍA



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