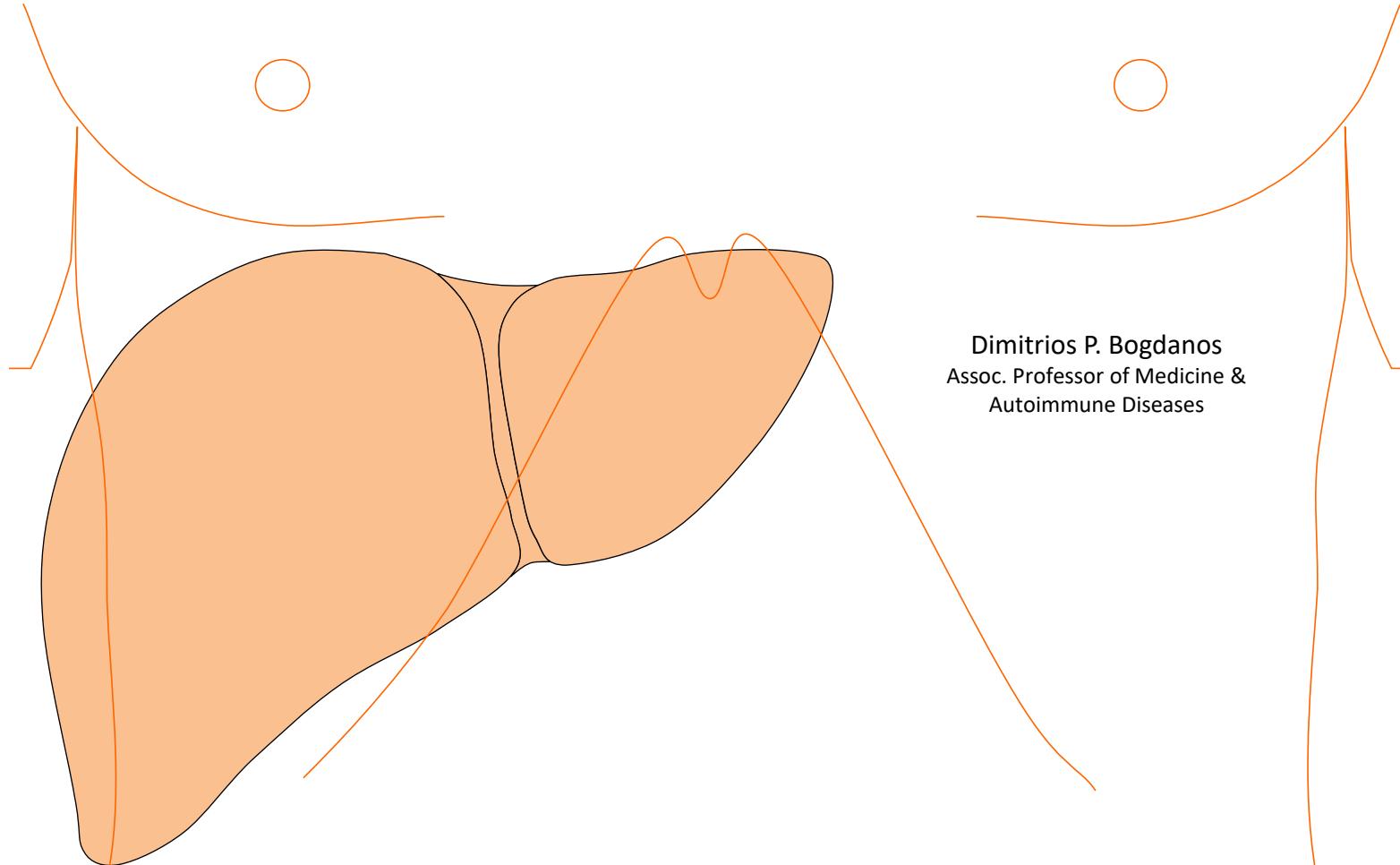


Autoimmune hepatitis vs liver involvement in autoimmune rheumatic diseases



Department of Rheumatology, Faculty of Medicine, University of Thessaly Medical School, Larissa, Greece
Division of Transplantation Immunology & Mucosal Biology, King's College London School of Medicine, UK



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Autoimmune Diseases

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College
LONDON

Ηπατική συμμετοχή στο ΣΕΛ: Βασικές γνώσεις (και γενικά στα APN)

- 1. Φάρμακα- Ηπατική Τοξικότητα**
- 2. Μη αλκοολική στεατοηπατίτιδα**
- 3. Αλκοολική ηπατίτιδα**
- 4. Ιογενής ηπατίτιδα (HBV ή HCV)**

Leggett BA J Gastroenterol Hepatol 1993;



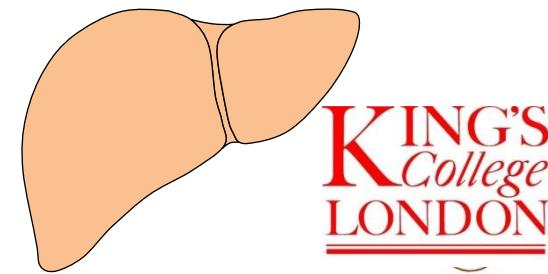
Autoimmune hepatitis vs liver involvement in autoimmune rheumatic diseases

Μπορεί ασθενής με αυτοάνοσο ρευματικό νόσημα να έχει
(αδιάγνωστη) αυτοάνοση ηπατίτιδα;

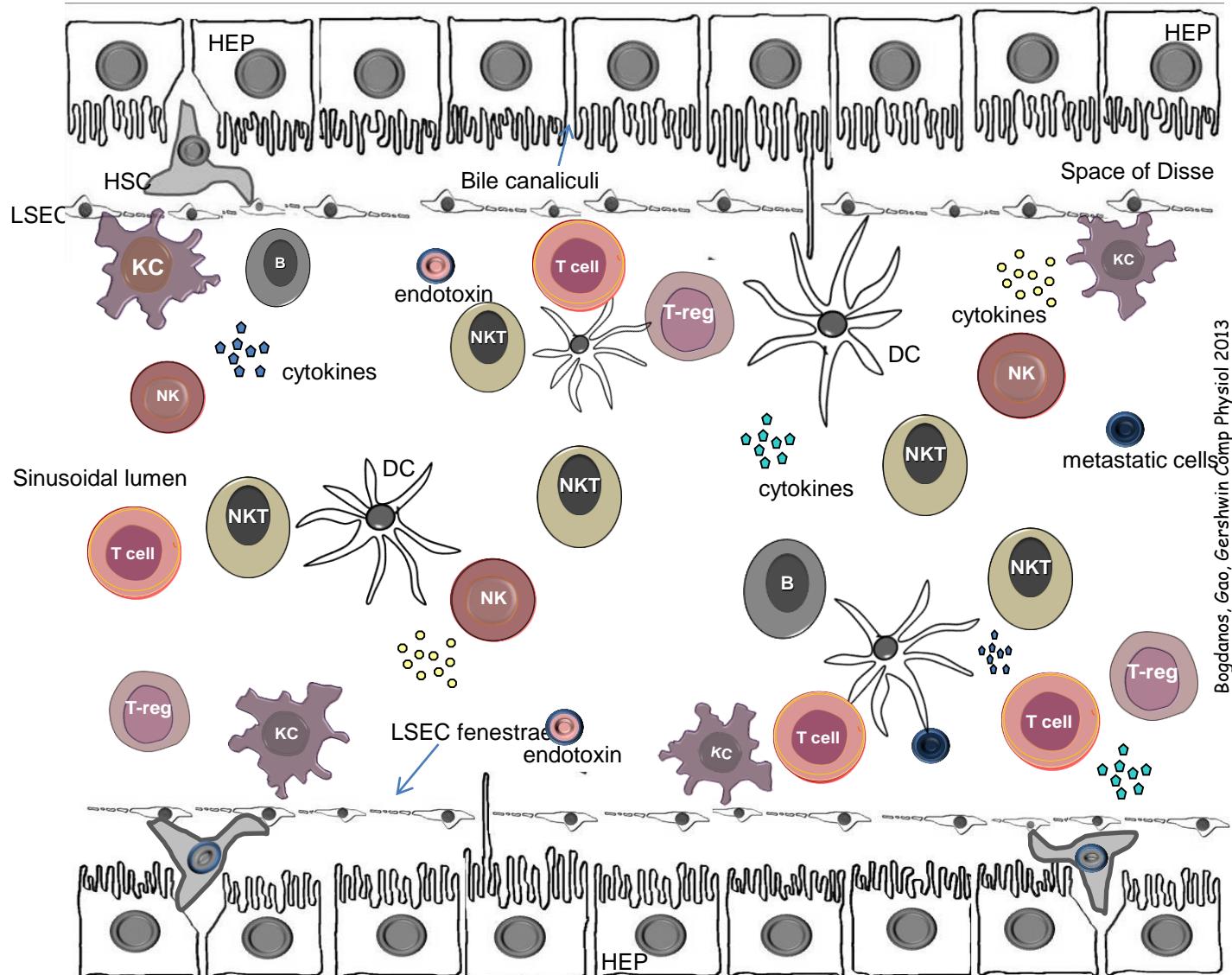
Το αντίστροφο (ARD σε AIH) πόσο συχνά μπορεί να συμβαίνει;

Αλλάζει καθόλου αυτό την θεραπευτική προσέγγιση;

Μπορεί να υπάρξει κάποιου είδους προσβολή του ήπατος σε
ασθενή με αυτοάνοσο ρευματικό νόσημα που να μην
σχετίζεται με την AIH;



The liver as a lymphoid organ: basics of liver immunology



Bogdanos, Gao, Gershwin *Comp Physiol* 2013



Αυτοάνοση Ηπατίτιδα (Autoimmune Hepatitis, AIH)

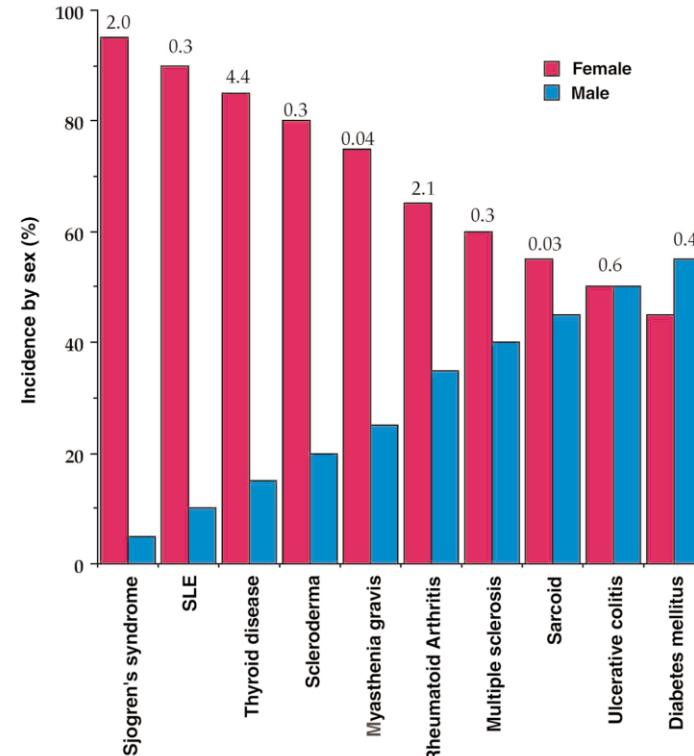
Συχνότητα: 10–25 per 100,000

Επιπολασμός: 1.5-2.9 per 100,000

Φύλο: Γυναίκες/Άνδρες 3:1 to 9:1)

Ετερογενής συμπτωματολογία

- Χωρίς ιδιαίτερα συμπτώματα
- χωρίς ειδικά συμπτώματα
- Οξεία ηπατίτιδα/οξεία ηπατική ανεπάρκεια (έως 20%)



Αυτοάνοση Ηπατίτιδα (Autoimmune Hepatitis, AIH)

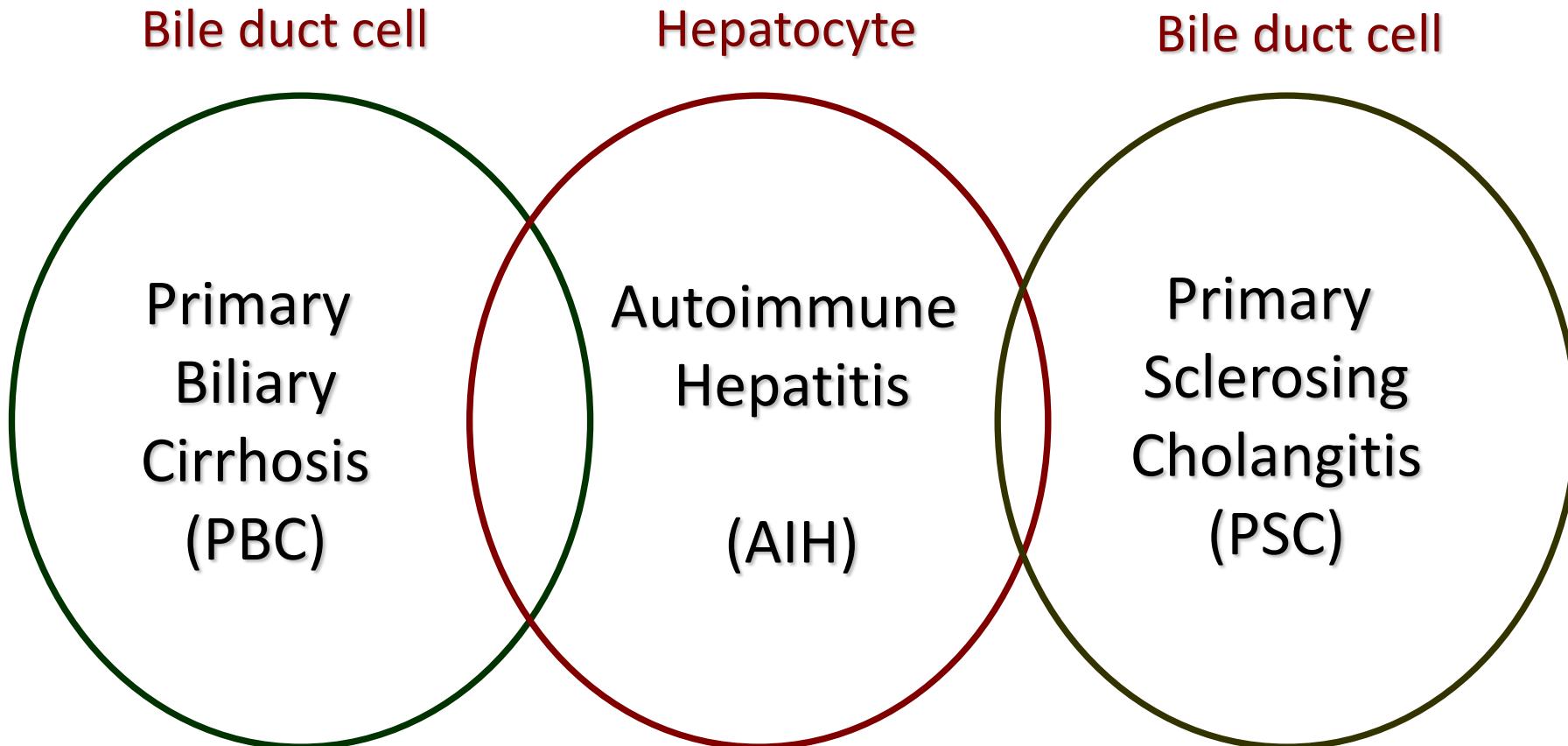
Δημογραφικά: ανεξάρτητα εθνικής προέλευσης & ηλικίας

Με ανοσοκαταστολή >80% των ασθενών επιβιώνουν, με καλή ποιότητα ζωής, χωρίς ανάγκη για μεταμόσχευση

Χωρίς ανοσοκαταστολή: φτωχή πρόγνωση, τελικού βαθμού κίρρωση σε <10 έτη



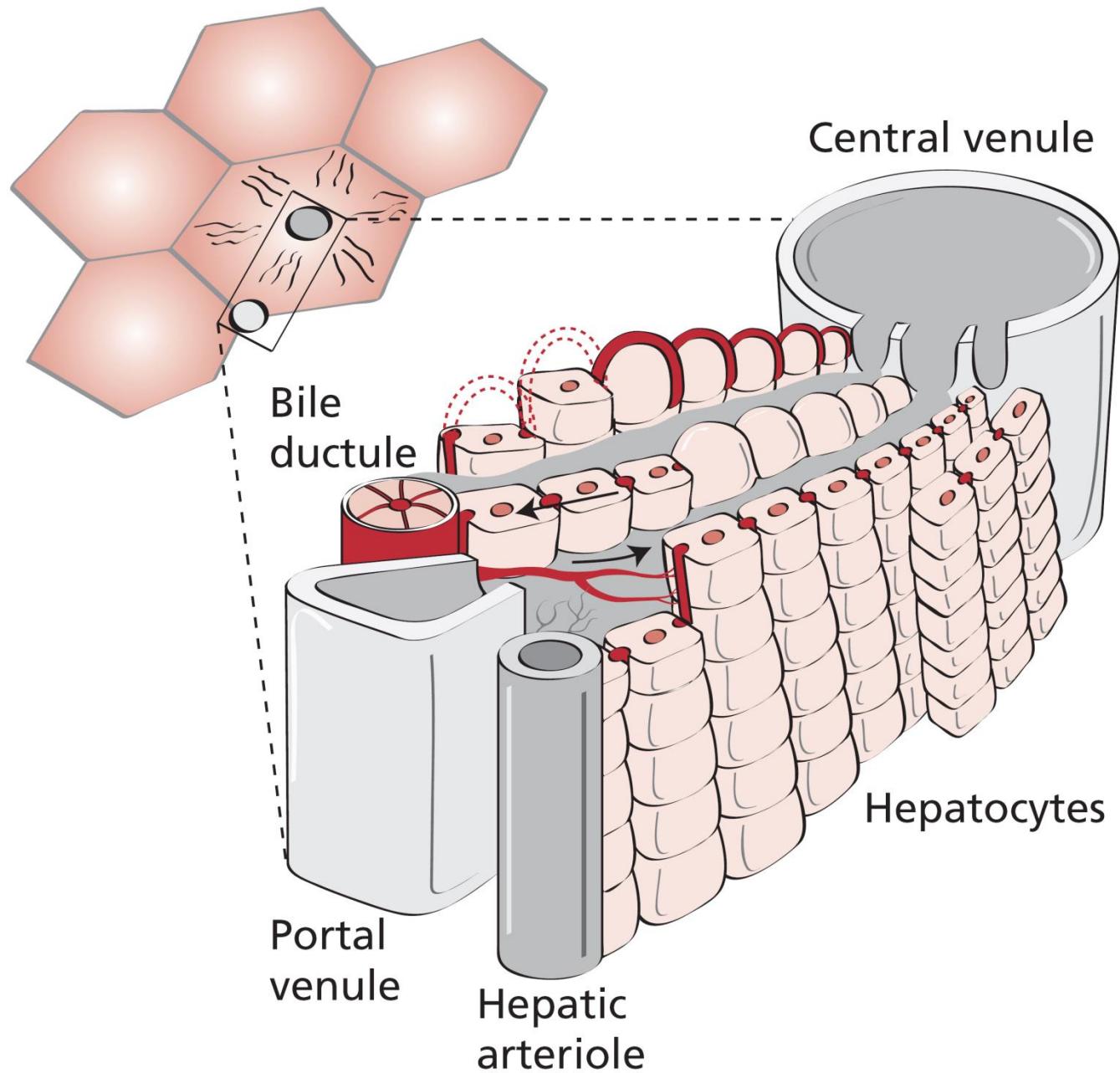
Overlapping Autoimmune Liver Disease

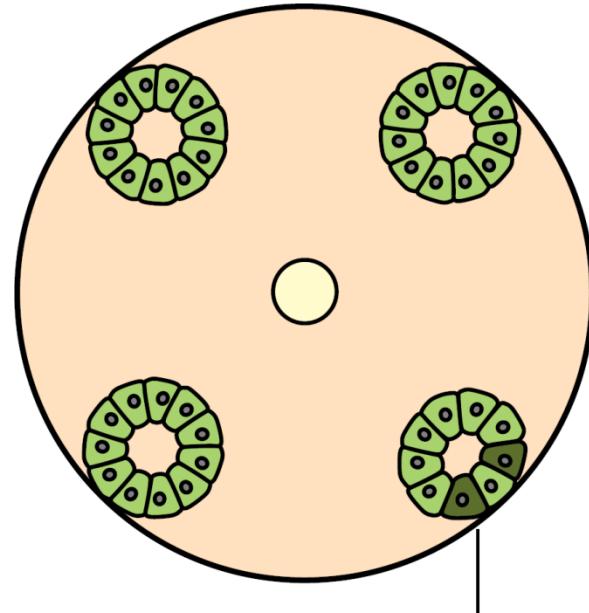


Vergani & Bogdanos Am J Gastroenterol 2003

Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis DO NOT co-exist

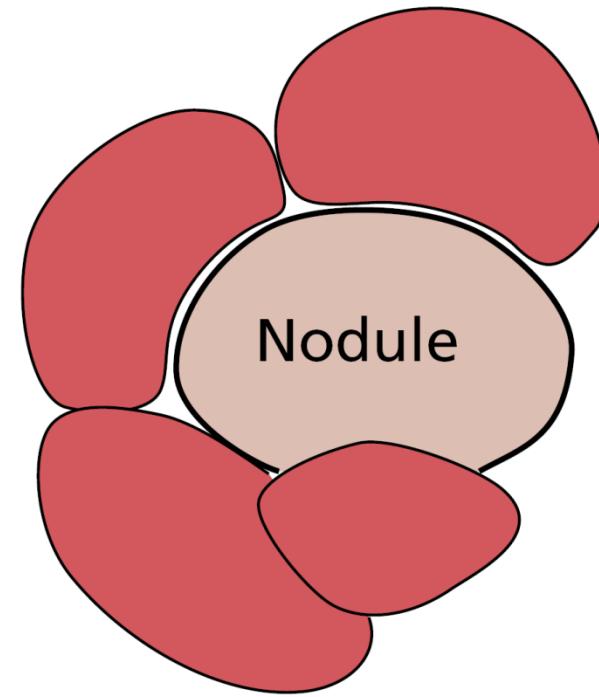






Damaged
bile duct

Time:
how long?



Cirrhosis





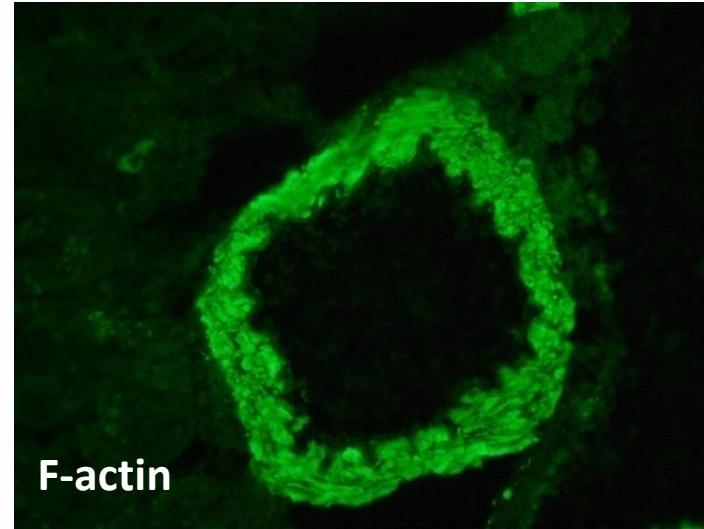
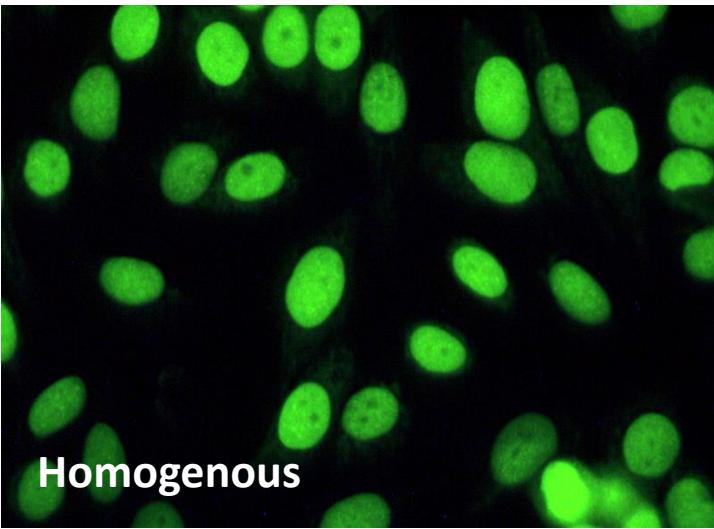
Απλοποιημένα κριτήρια αυτοάνοσης ηπατίτιδας

Table 2. Simplified Diagnostic Criteria for Autoimmune Hepatitis

Variable	Cutoff	Points
ANA or SMA	≥1:40	1
ANA or SMA or LKM or SLA	≥1:80	2*
IgG	≥1:40	1
	>Upper normal limit	1
	>1.10 times upper normal limit	2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH Typical AIH	1 2
Absence of viral hepatitis	Yes	2
Οριστική Διάγνωση ≥ 7		≥6: probable AIH
Πιθανή Διάγνωση: 6		≥7: definite AIH

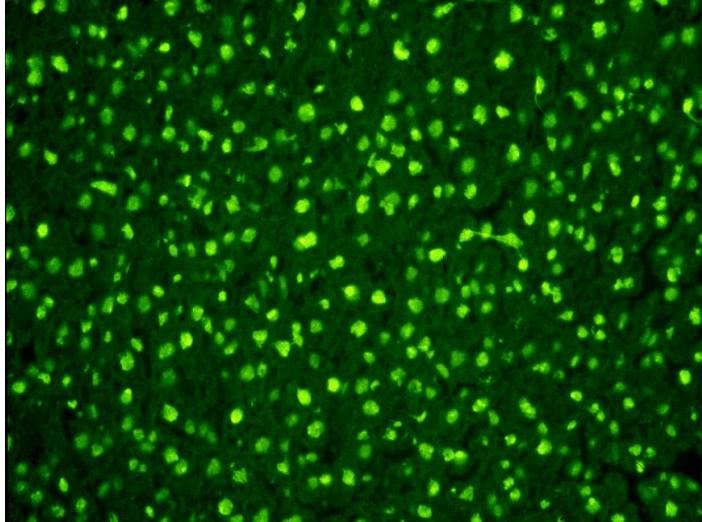
*Addition of points achieved for all autoantibodies (maximum, 2 points).

Autoimmune Hepatitis - Type 1



Anti-nuclear (ANA) antibodies and/or Anti-smooth muscle antibodies (SMA)

Autoimmune Hepatitis - Type 1



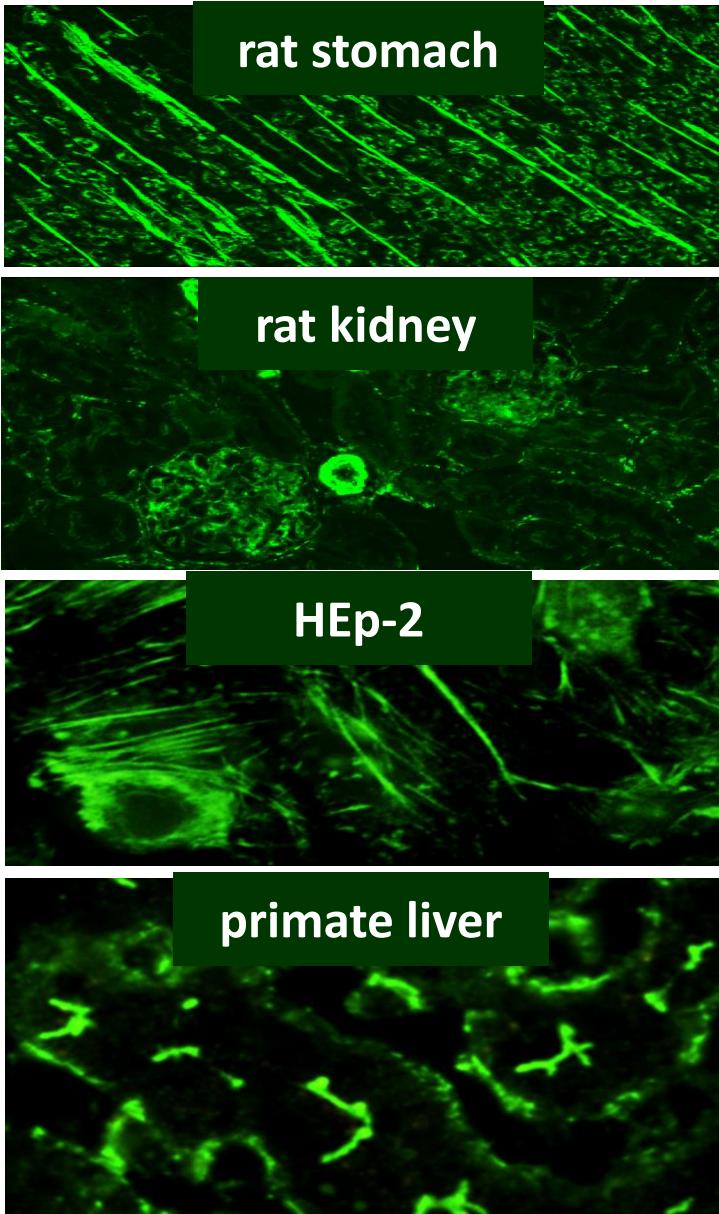
Anti-nuclear (ANA) antibodies

No single AIH-1 specific ANA antigen

Targets:

- dsDNA
- Histones
- Ribonucleoproteins
- Chromatin
- Centromere
- Ribosomal P

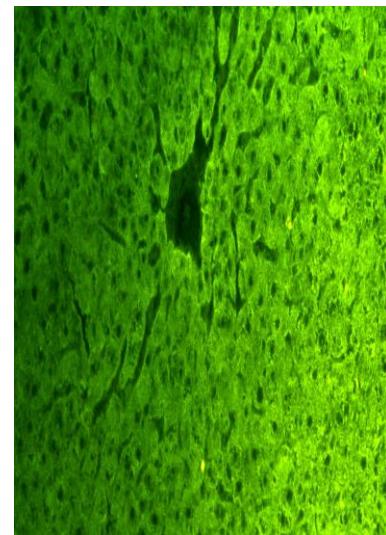
Smooth Muscle Antibodies (SMA): AIH-1



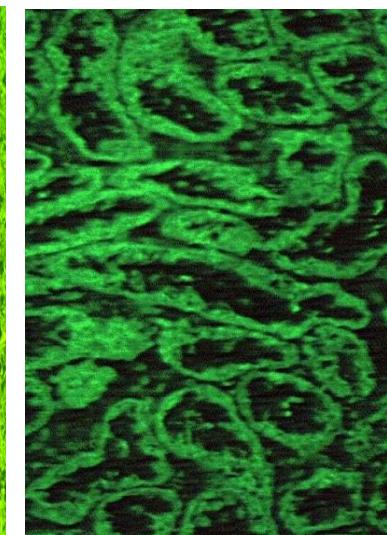
- Detection: IFT (VGT pattern)
- Prevalence: 30-85%
- Target antigens: F-actin, various often MF
- High titers SMA and ANA suggest AIH
- Also associated with viral hepatitis and other liver and non-liver related diseases e.g HCV

Autoimmune Hepatitis - Type 2

Liver

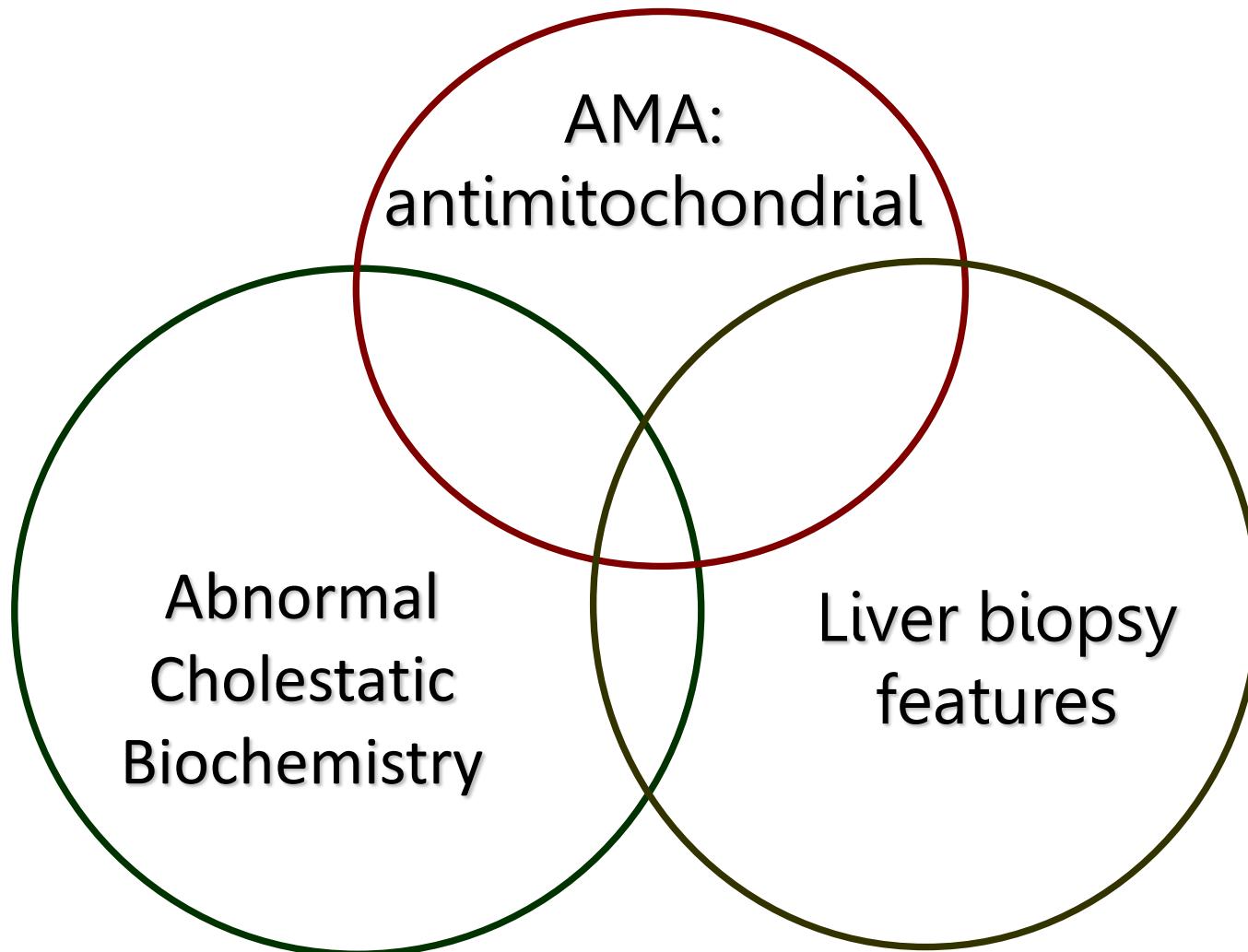


Kidney

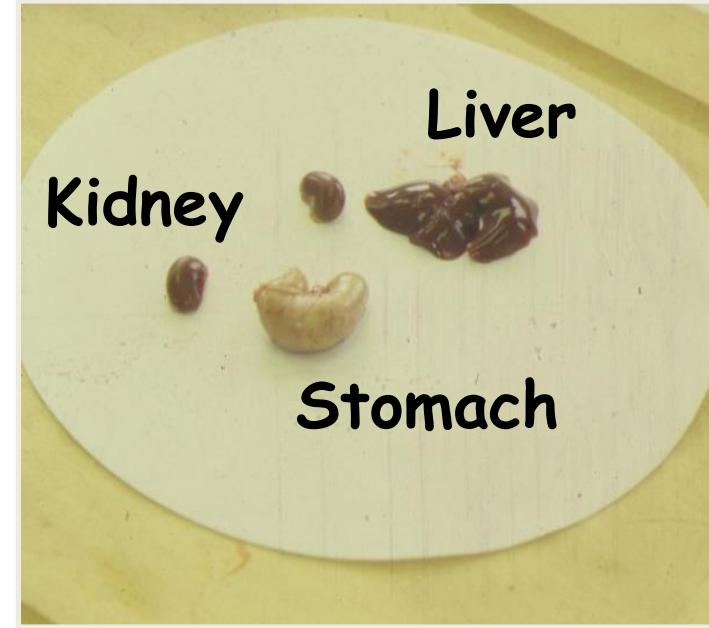
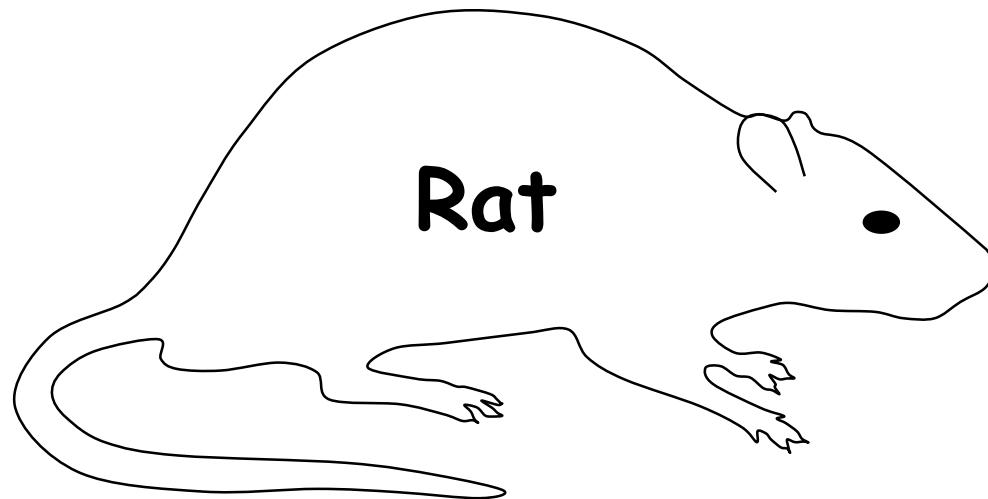


Anti-Liver Kidney Microsomal antibody type 1 antibody

Primary Biliary Cirrhosis: DIAGNOSIS

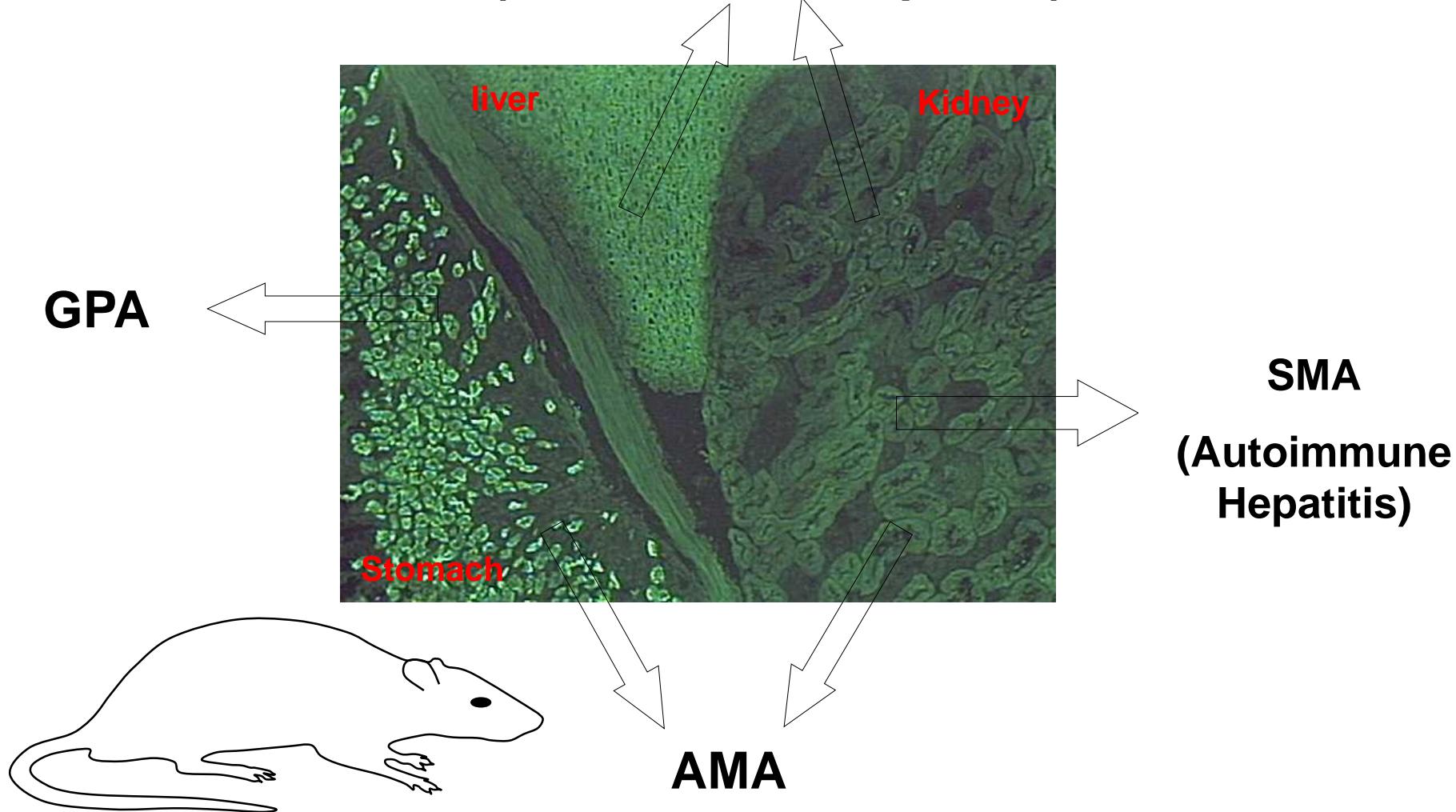


Diagnosis of Primary Biliary Cirrhosis: Anti-mitochondrial antibodies



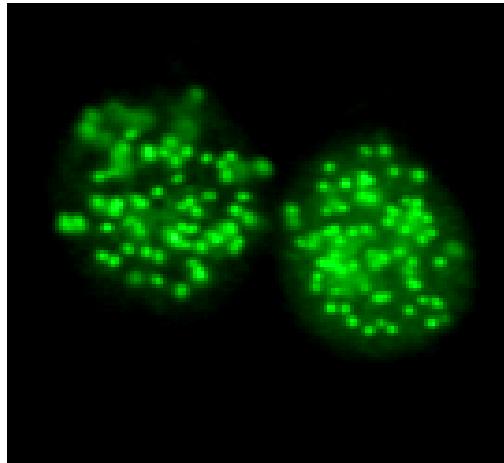
Diagnosis of Primary Biliary Cirrhosis: Anti-mitochondrial antibodies

LKM-1 (Autoimmune Hepatitis)

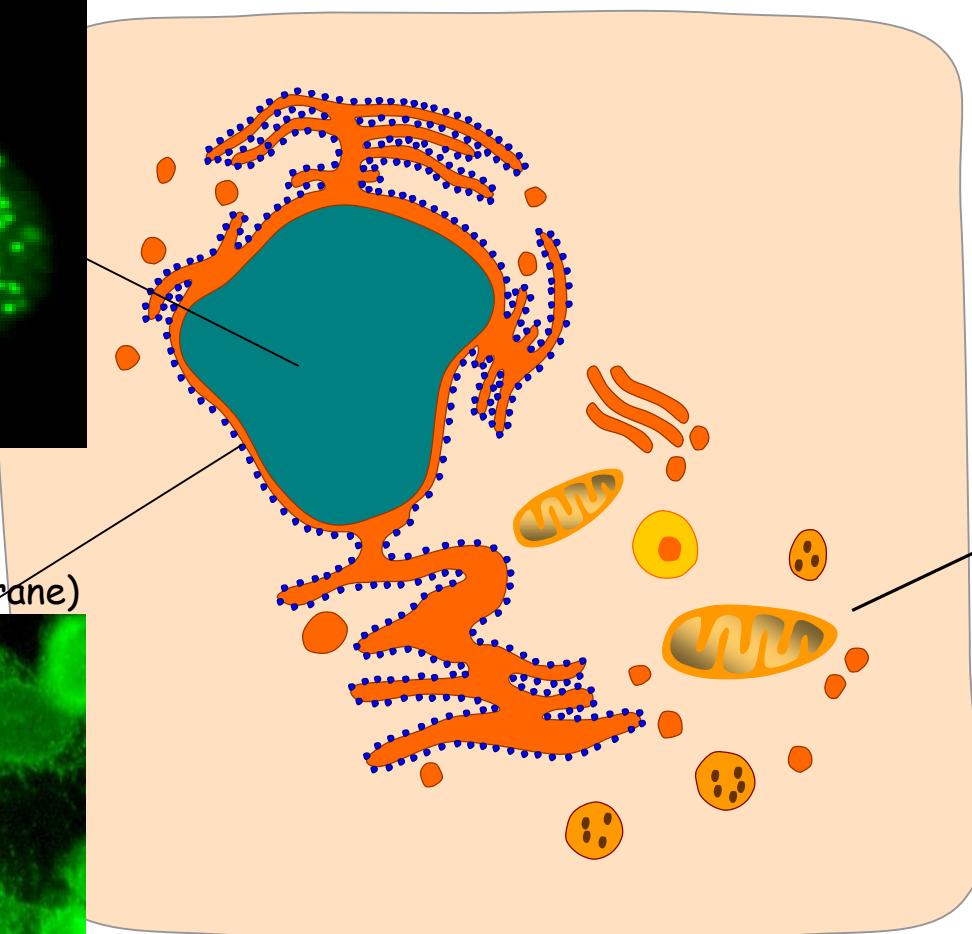
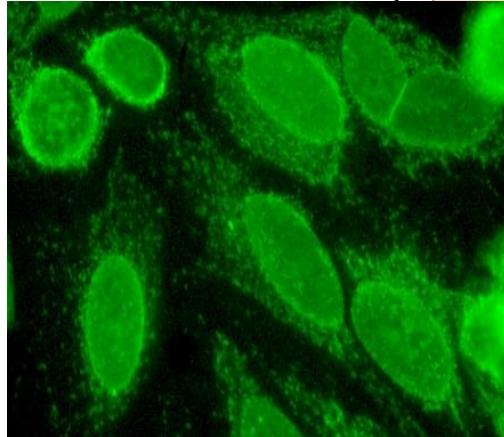


Additional serological markers of Primary Biliary Cirrhosis: Disease-specific anti-nuclear antibodies (ANA)

Nuclear Dots (Nuclear body)



Rim Like (Nuclear membrane)



BILIARY EPITHELIAL CELL

Mitochondrion

Autoimmune hepatitis vs liver involvement in autoimmune rheumatic diseases

Table 1. Histopathology of liver involvement in systemic rheumatic diseases

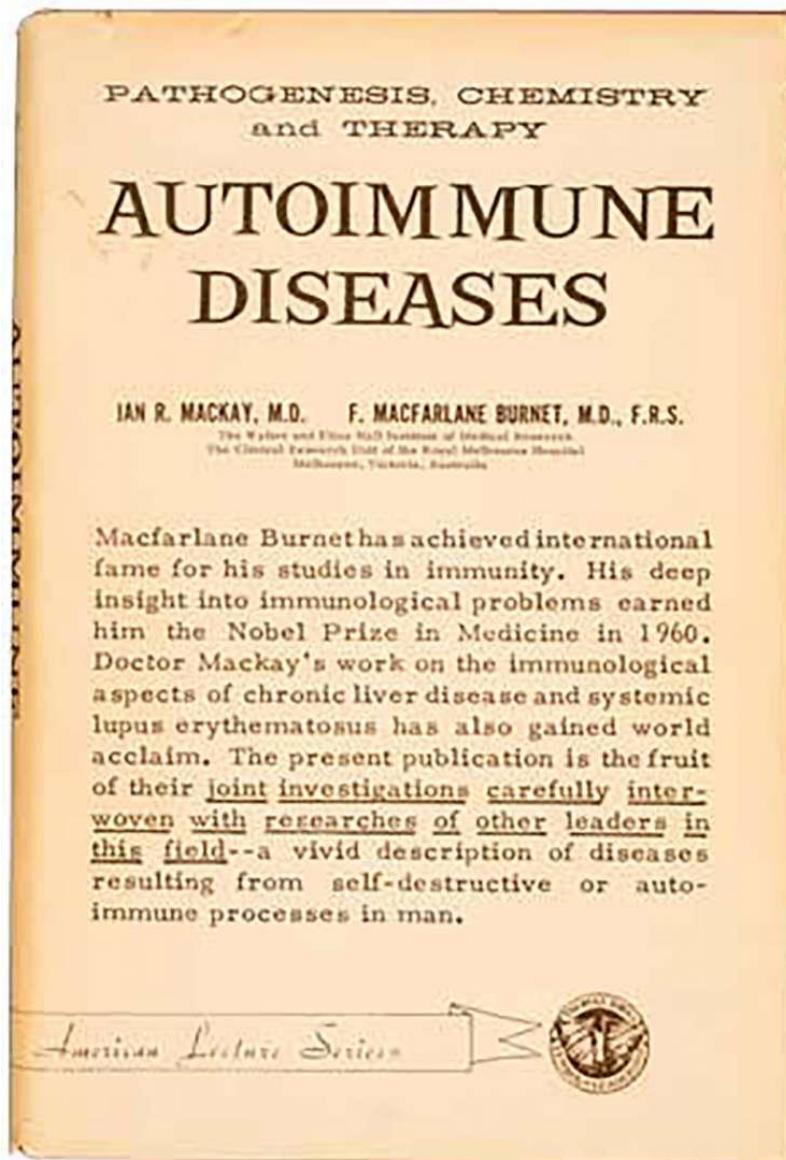
Histological definition	Features
Chronic active hepatitis	Piecemeal necrosis with mononuclear cell infiltrate
Chronic persistent hepatitis	Chronic inflammatory infiltration of the portal tract with preserved lobular architecture and without portal fibrosis
Cirrhosis	Diffuse liver degeneration characterized by fibrous tissue and regenerative nodules
Fibrosis	Abnormal production of fibrous tissue in response to liver injury
Steatosis	Abnormal retention of lipids within hepatocytes
Cholangitis	Inflammation of bile ducts
Reactive hepatitis	Aspecific and mild inflammatory cell infiltrate of portal spaces
Nodular regenerative hyperplasia	Diffuse nodularity of the liver without fibrosis
Granulomas	Aggregate of epithelioid cells surrounded by lymphocytes
Idiopathic portal hypertension	Increased blood pressure in the veins of the portal system not due to liver diseases
Arteritis	Vessel wall inflammation
Giant cell hepatitis	Presence throughout the liver of enlarged multinucleated hepatocytes with abundant cytoplasm
Massive hepatic necrosis	Diffuse hepatocyte necrosis





Melbourne 1962

Mackay and Burnet (1962) The first book on autoimmune diseases





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doi:10.3748/wjg.14.3374



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World Journal of Gastroenterology ISSN 1007-9327
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TOPIC HIGHLIGHT

Pietro Invernizzi, MD; Ian R Mackay, MD, Series Editor

Autoimmune liver serology: Current diagnostic and clinical challenges

Dimitrios P Bogdanos, Pietro Invernizzi, Ian R Mackay, Diego Vergani

LUPOID HEPATITIS

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ROYAL MELBOURNE HOSPITAL, VICTORIA, AUSTRALIA

Lancet 1956

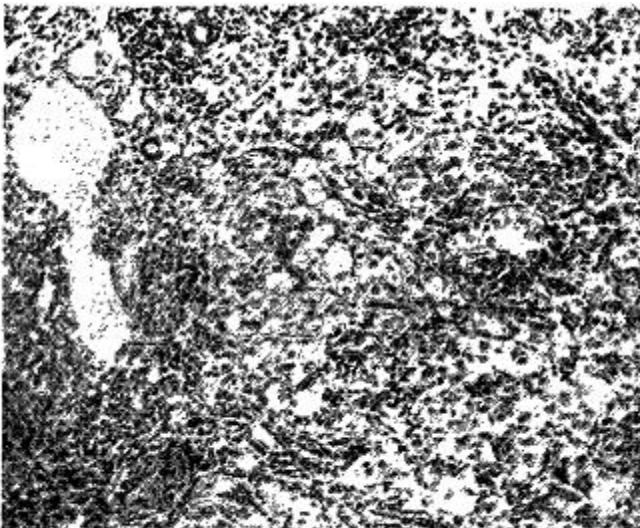
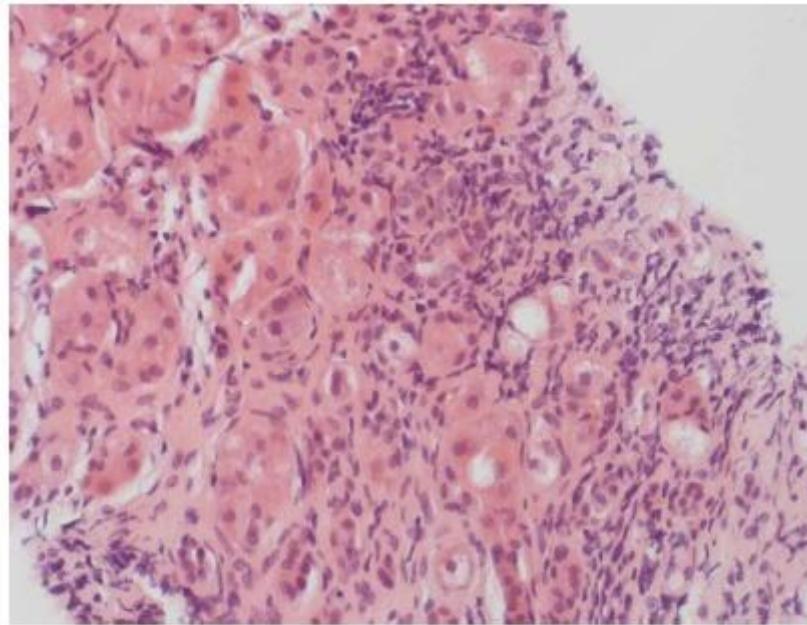


Fig. 1—Case 1 : liver biopsy (February, 1954) showing intense lymphoid infiltration and nodular regeneration of polygonal cells ($\times 150$).

Case no.	Sex	Age (yr.)	Date	FEATURES OF LUPOID HEPATITIS										Liver		
				Serum-albumin (mg. per 100 ml.)	Cephalin flocculation	Serum-albumin (g. per 100 ml.)	Serum-globulin (g. per 100 ml.)	Serum-globulin (g. per 100 ml.)	Serum-alanine-phosphatase (K-A. units)	Prothrombin-time (% of normal)	Test for L.E. cells	E.S.R. (mm. in 1 hr.)	Parenchyma	Fibrous tissue	Cellular infiltration*	
1	F	20	April, 1953	5·0	+++	3·6	5·5	3·4	21	49	..	80	Normal structure, cell necrosis, regeneration	Not increased	+++	
			June, 1953	12·5	++	3·3	6·0	4·2	25	45	Active nodular regeneration	+	++	
			Feb., 1954	1·7	++	3·1	4·7	3·4	15	73	Active nodular regeneration	++	++	
			Nov., 1955	3·2	++	2·5	3·9	2·8	77	..	Positive	73	Nodular regeneration	++	..	
2	F	21	June, 1956	1·1	++	2·7	3·3	1·9	83	25	Negative	86	
			March, 1955	4·8	++	2·3	4·4	3·7	22	50	Positive	102	Active nodular regeneration	++	++	
			Jan., 1956	3·7	++	2·9	3·3	2·0	17	27	Negative	19	Active nodular regeneration	++	++	
			June, 1952	3·5	++	2·8	4·4	2·0	8	64	Active nodular regeneration, accumulation of fat	++	++	
4	F	66	April, 1954	12·5	++	3·0	5·8	3·6	31	24	
			Nov., 1955	5·6	++	2·6	4·4	2·7	40	12	Positive	73	
			Nov., 1955	0·6	++	2·3	3·9	2·1	17	100	Positive	106	Nodular regeneration	++	+	
			June, 1956	0·6	++	3·0	3·2	1·8	12	..	Negative	129	Nodular regeneration	++	..	
5	M	16	Aug., 1956	0·6	++	2·1	2·8	1·4	10	36	(Necropsy findings)	++	+	
			Jan., 1955	2·0	++	3·2	4·2	3·0	27	64	Positive	..	Active nodular regeneration, giant multinucleate cells	++	++	
6	F	75	July, 1956	0·6	..	3·6	4·0	1·8	33	75	Negative	37	
			Sept., 1955	8·8	++	1·9	5·4	2·6	20	64	Positive	..	Active nodular regeneration	++	++	
7	F	37	Nov., 1954	2·8	++	3·4	5·1	4·3	17	100	Normal structure, cell regeneration	++	++	
			Jan., 1955	1·5	++	3·3	4·7	3·1	17	..	Positive	76	
			May, 1956	0·2	++	3·7	3·3	2·0	14	..	Positive	63	

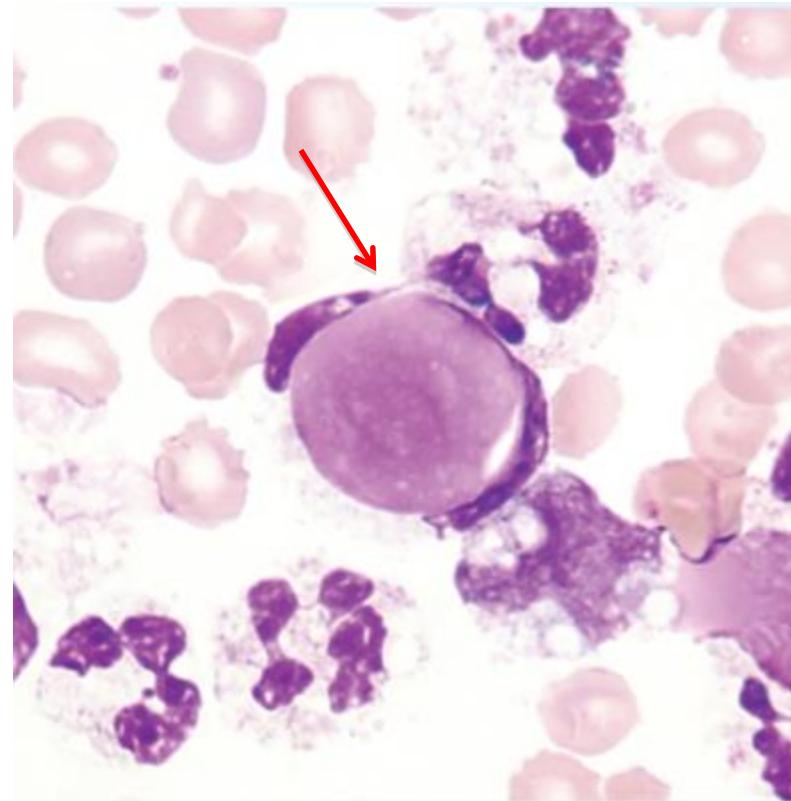
* Predominantly lymphocytes, plasma-cells, and histiocytes.

Τυπική ιστοπαθολογική εικόνα αυτοάνοσης ηπατίτιδας





LE cell



LUPOID HEPATITIS AND THE HEPATIC LESIONS OF SYSTEMIC LUPUS ERYTHEMATOSUS

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ASSISTANT TO THE CLINICAL RESEARCH UNIT

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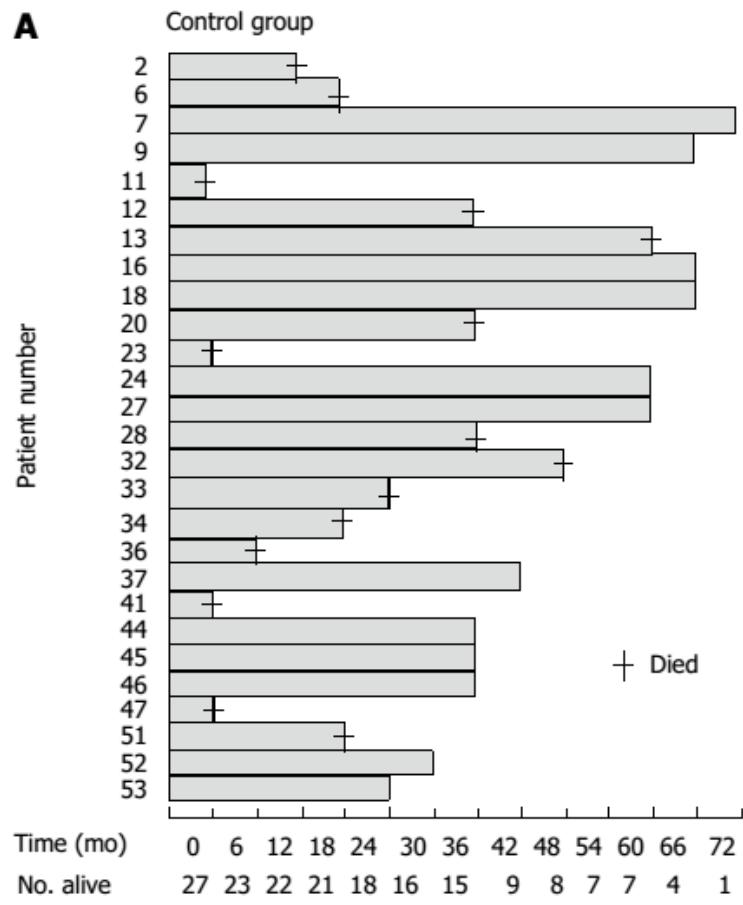
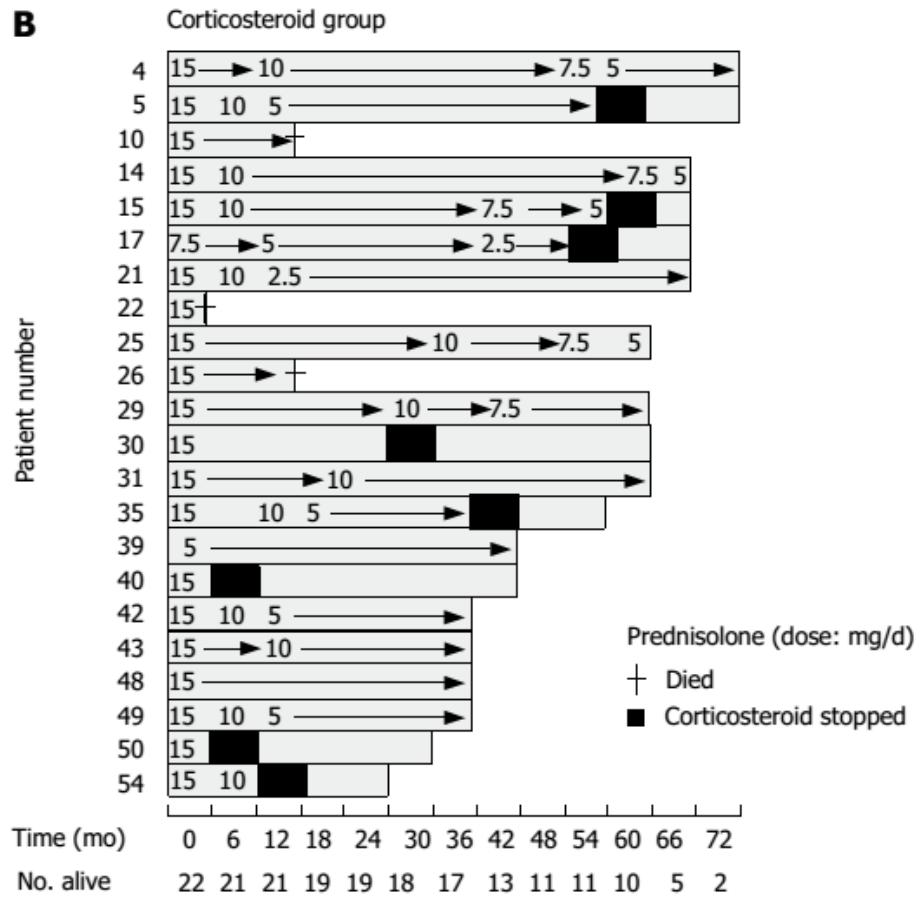
A POSITIVE lupus erythematosus (L.E.) cell test may be obtained in cases of chronic hepatitis and cirrhosis (Joske and King 1955, Mackay et al. 1956, Wilkinson and Sacker 1957). We called this syndrome "lupoid hepatitis" and suggested that the L.E. phenomenon, rather than being a "non-specific" or "false positive" reaction, might represent evidence for abnormal antibody formation in chronic hepatitis; in turn, this may be responsible for the downward progress of the disease, and also for certain other lupus manifestations which may supervene in lupoid hepatitis (Taft et al. 1958).

We have attempted to assess the relationship of lupoid hepatitis to systemic lupus erythematosus (S.L.E.) by (a)

* Working with the aid of a grant from the National Health and Medical Research Council of Australia.



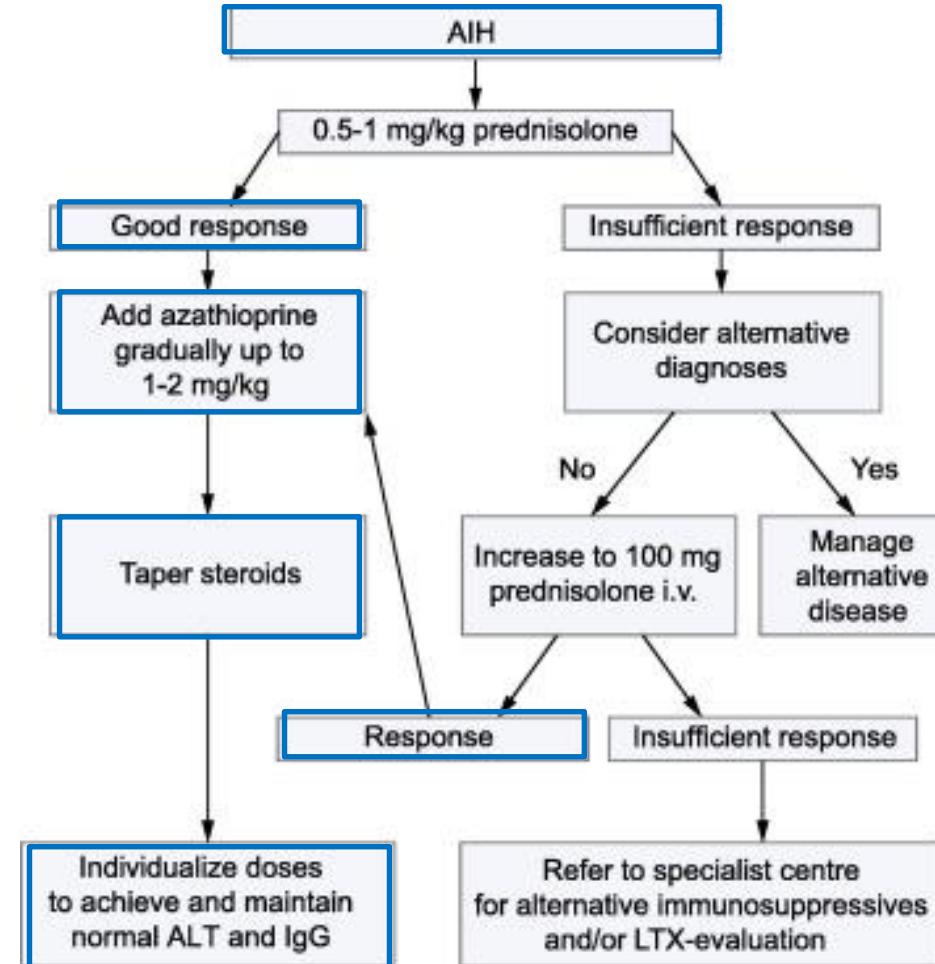
Fig. 1—Woman, aged 29 (case L.H. 3) with nutritional hepatitis and positive L.E.-cell test, showing the rash of lupus erythematosus.

A**B**

Q J Med 1971



Therapeutic algorithm for autoimmune hepatitis when starting with prednisolone monotherapy



Manns J Hepatol 2015

Lupoid hepatitis (autoimmune hepatitis)

vs

lupus hepatitis

The Liver in Systemic Lupus Erythematosus: Pathologic Analysis of 52 Cases and Review of Japanese Autopsy Registry Data

TOSHIHARU MATSUMOTO, MD, TUGIO YOSHIMINE, MD,
KOUJI SHIMOUCHI, PhD, HIDETOSHI SHIOTU, MD,
NORIYUKI KUWABARA, MD, YOSHIRO FUKUDA, MD,
AND TANJI HOSHI, MD Human Pathology 1992

TABLE 2. Incidence of Liver Diseases in Patients
With Systemic Lupus Erythematosus Recorded
in the Japanese Autopsy Registry Data (n = 1,468)

Liver Disease	No. of Patients	Percentage of Patients
Fatty liver	169	11.5
Hepatic congestion	87	5.9
Chronic liver diseases		
Chronic hepatitis	36	2.4
Cirrhosis	17	1.1
Liver fibrosis	12	0.8
Tuberculosis	27	1.8
Hemangioma	23	1.5
Fungus infection	11	0.7
Liver abscess	10	0.6
Hepatic infarction	8	0.5
Nodular regenerative hyperplasia of the liver	5	0.3
Acute hepatitis	5	0.3
Fulminating hepatitis	5	0.3
Cytomegalic inclusion disease	5	0.3



Ηπατική συμμετοχή στο ΣΕΛ

Ο όρος υποκλινική ηπατοπάθεια χρησιμοποιήθηκε το 1981 για
να περιγράψει την κύρια αιτία διαταραχής ηπατικής βιοχημείας στο ΣΕΛ

Gibson J Rheumatol 1981



Ηπατική συμμετοχή στο ΣΕΛ

Αυτοάνοση ηπατίτιδα (Πότε να τη σκεφτούμε –Πως να την αποκλείσουμε)

Leggett BA J Gastroenterol Hepatol 1993;



KING'S
College
LONDON

Autoimmune hepatitis vs liver involvement in autoimmune rheumatic diseases

Μπορεί ασθενής με ΣΕΛ να έχει (αδιάγνωστη)
αυτοάνοση ηπατίτιδα;

Autoimmune liver related autoantibodies are present in
approx 40% of patients with SLE

Li et al Clin Chim Acta 2006

The Chinese patients with SLE were misdiagnosed as
SLE and were true AIH patients

Bogdanos Clin Chim Acta 2006



Autoimmune hepatitis vs liver involvement in autoimmune rheumatic diseases

Μπορεί ασθενής με ΣΕΛ να έχει co-existent (and overlapping αλλά αδιάγνωστη) αυτοάνοση ηπατίτιδα;

Prevalence of liver injury in the most common connective tissue diseases.

Disease	Enzyme alterations	Biochemical profile	Histologic alterations
Sjogren's syndrome	50%	cholestatic > hepatocellular	18%
SLE	30%	cholestatic < hepatocellular	20%
Systemic sclerosis	1%	cholestatic > hepatocellular	9%

De Santis BPRP Gastroenterol 2013

Ναι, αλλά πόσο συχνό είναι ώστε να μας προβληματίσει;

Liberal and Bogdanos Clin Res Hepatol Gastroenterol 2013



TABLE 2. Concurrent Autoimmune Diseases in Our Cohort of 278 Patients With Autoimmune Hepatitis

Concurrent Autoimmune Diseases	No. Patients	Percentage
Total no. concurrent autoimmune diseases	140	
Total patients with concurrent autoimmune diseases	111*	40*
AIH/PBC or AIH/PSC overlap	72	26
Autoimmune thyroid diseases		
Hashimoto thyroiditis	20	7.2
Grave disease	5	1.8
Unspecified autoimmune thyroiditis	3	1.1
Vitiligo	5	1.8
Rheumatoid arthritis	5	1.8
Sjogren syndrome	4	1.4
Ulcerative colitis	4	1.4
Conjunctivitis	4	1.4
Celiac disease	3	1.1
Systemic lupus erythematoses	2	0.7
Type I diabetes	2	0.7
Multiple sclerosis	2	0.7
Polymyalgia rheumatica	2	0.7
Urticaria	2	0.7
Crohn's disease	1	0.4
Autoimmune gastritis	1	0.4
Collagenous colitis	1	0.4
Hypophysitis	1	0.4
Sarcoidosis	1	0.4



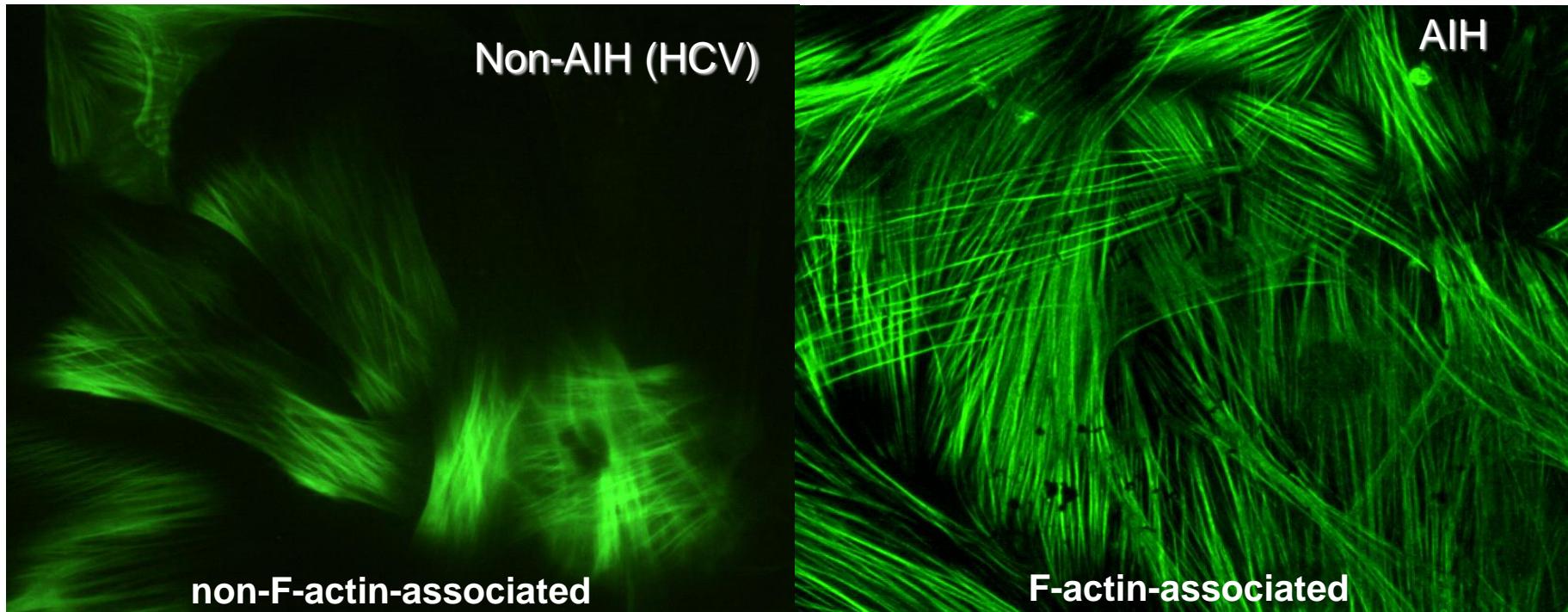
Πόσο συχνά ασθενής με αυτοάνοσο ρευματικό νόσημα έχει (αδιάγνωστη) αυτοάνοση ηπατίτιδα;

Prevalence of autoimmune liver disease in connective tissue diseases.

	PBC	AIH	PSC
SLE	2.7–15%	2.7–20%	1 case
aPL	1 case	4 cases	1 case
pSS	35–57%	6–47%	11 cases
SSc	51.2%	11 cases	1 case
PM/DM/AS	14.3%	7.1%	–

De Santis BPRP Bastroenterol 2013

SMA in AIH vs SMA in non-AIH diseases





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Hepatology Research 28 (2004) 137–139

**Hepatology
Research**

www.elsevier.com/locate/ihepcom

Preliminary notes

High frequency of anti-ribosomal P antibody in patients with systemic lupus erythematosus-associated hepatitis

Hiromasa Ohira ^{a,*}, Junko Takiguchi ^b, Tsuyoshi Rai ^a, Kazumichi Abe ^a,
Junko Yokokawa ^a, Yukio Sato ^a, Isao Takeda ^a, Takashi Kanno ^b

^a Department of Internal Medicine II, Fukushima Medical University School of Medicine,
1 Hikarigaoka, Fukushima 960-1295, Japan

^b Division of Rheumatology, Ohta Nishinouchi Hospital, Koriyama, Japan

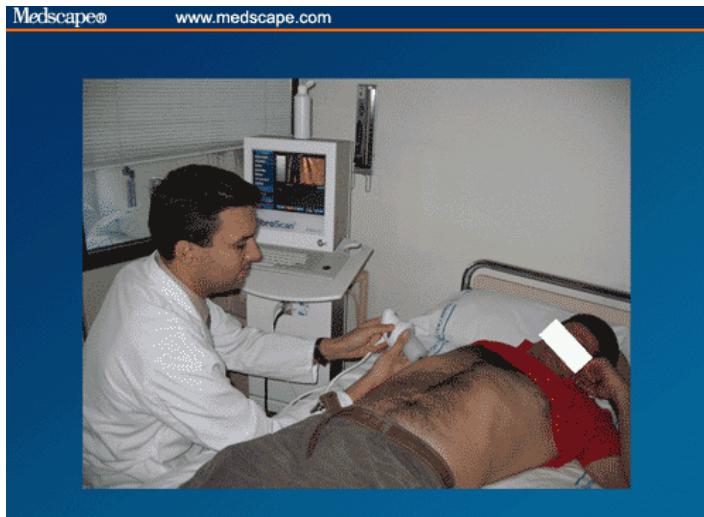
Received 30 June 2003; received in revised form 24 October 2003; accepted 19 November 2003

Accepted 16 December 2003; available online 24 October 2003; accepted 16 November 2003

Editorial office: www.elsevier.com/locate/ihepcom

	Ribosomal P antibody positive ratio (%)	Renal dysfunction (positive number)	CNS lupus (positive number)	T-Bil (mg/dl)	ALT (IU/l)	ALP (IU/l)	IgG (mg/dl)
Systemic lupus erythematosus (<i>n</i> = 61)							
SLE-associated hepatitis (<i>n</i> = 16)	11 (68.8) ^a	2 (0)	0 (0)	1.0 ± 0.9	476.1 ± 1382.4	485.5 ± 470.4	1941.3 ± 641.7
Fatty liver (<i>n</i> = 7)	2 (28.6) ^b	4 (2)	2 (0)	0.8 ± 0.4	53.3 ± 25.5	231.5 ± 98.8	1764.2 ± 220.1
Drug-induced hepatitis (<i>n</i> = 6)	1 (16.7)	1 (1)	4 (1)	0.6 ± 0.3	57.8 ± 62.6	515.5 ± 361.4	1495.3 ± 926.6
With autoimmune hepatitis (<i>n</i> = 5)	1 (20.0) ^{c,e}	3 (1)	1 (0)	3.9 ± 6.7*	362.0 ± 404.3	383.2 ± 133.2	3266.6 ± 1187.5*
No liver dysfunction (<i>n</i> = 27)	8 (29.6) ^{d,f}	11 (2)	1 (0)	0.5 ± 0.3	22.3 ± 15.7*	178.4 ± 76.1*	1978.5 ± 849.2
Autoimmune hepatitis (<i>n</i> = 20)	0 (0)	0 (0)	0 (0)	5.9 ± 10.9*	522.9 ± 1382.4	411.1 ± 242.7	3139.0 ± 1002.9*

Assessment of liver fibrosis with transient elastography in autoimmune rheumatic diseases with undiagnosed liver injury



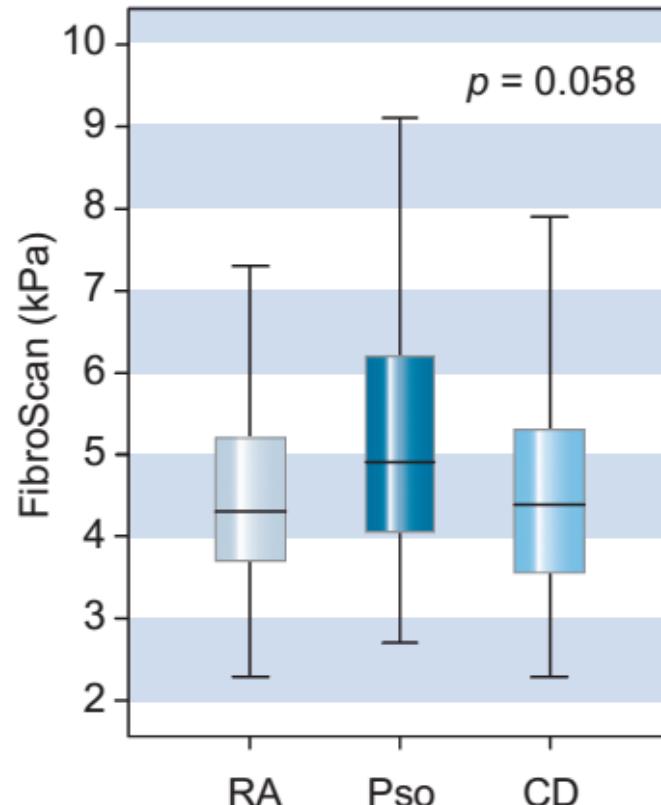
Προσοχή: Όχι σε οξεία ηπατίτιδα

Laharie J Hepatol 2010



Assessment of liver fibrosis with transient elastography in patients treated with methotrexate

44/518 (8.5%) pts had Fibroscan test suggesting severe liver fibrosis



Multivariate analysis

Metabolic syndrome	1.17	0.40 – 3.42	0.77
Alcohol >14 drinks/week	2.95	1.11 – 7.80	0.03
Psoriasis	1.58	0.60 – 4.10	0.35
BMI >28 kg/m ²	5.33	1.92 – 14.78	0.01

Laharie J Hepatol 2010



Assessment of liver fibrosis with transient elastography in patients treated with methotrexate

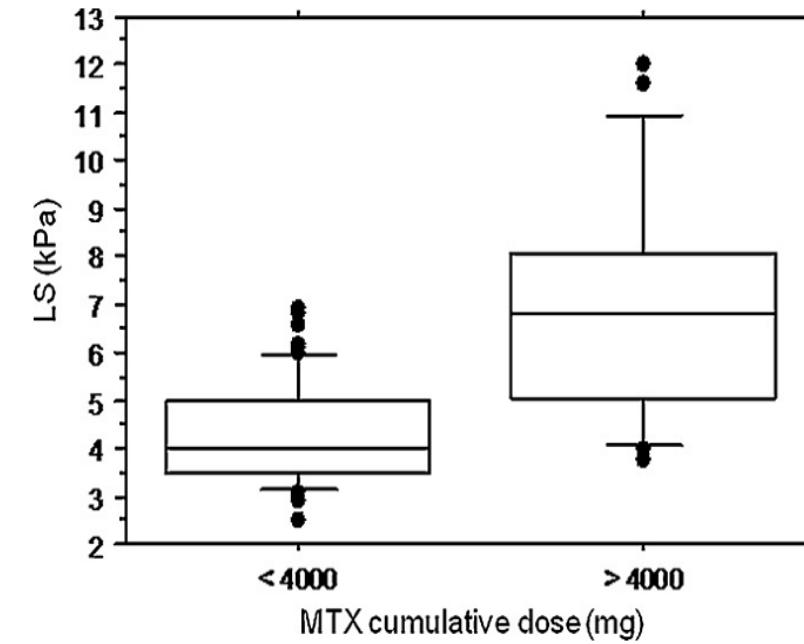
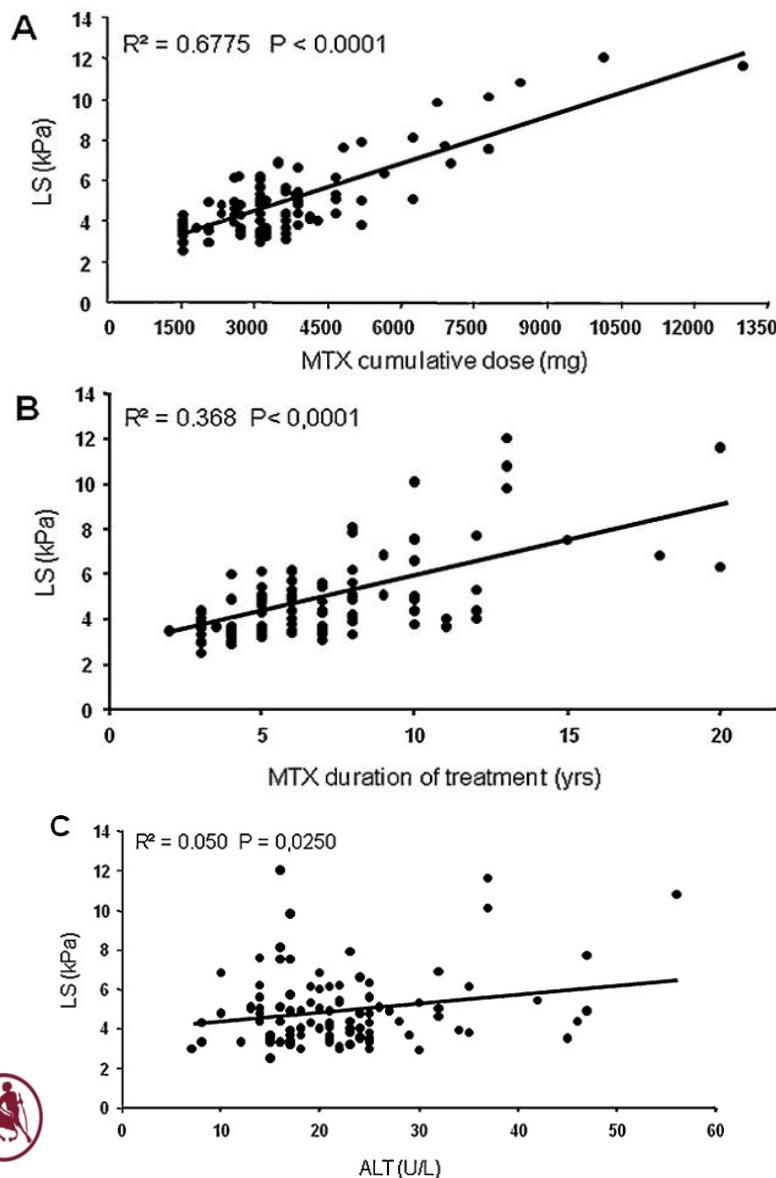
	Whole population	Cases	Controls	p
n	518	390	128	
Median FibroScan (kPa)	4.6 (3.7 - 5.6)	4.6 (3.7 - 5.6)	4.4 (3.8 - 5.6)	NS
Median FibroTest	0.16 (0.08 - 0.27)	0.16 (0.08 - 0.26)	0.17 (0.09 - 0.3)	NS

	MTX >1500 mg	MTX ≤1500 mg	p
n	176	342	
Median FibroScan (kPa)	4.6 (3.6 - 5.8)	4.6 (3.8 - 5.4)	NS
Median FibroTest	0.17 (0.09 - 0.3)	0.15 (0.08 - 0.25)	NS

Laharie J Hepatol 2010



Liver stiffness correlates with methotrexate cumulative dose in patients with rheumatoid arthritis



Arena Dig Liv Dis 2012

Πότε θα κάνεις βιοψία ήπατος;

- Αυξημένη IgG
- ANA(+)/ SMA(+) F-actin
- Ιογενείς Ηπατίτιδες (-)

Πιθανή ΑΙΗ

- Όταν έχουν αποκλειστεί όλα τα άλλα
- Όταν εμφανίζεται ως οξεία ηπατίτιδα
- Προσοχή: Όχι σε μη αντιρροπούμενη κίρρωση



Overlapping AiRD-autoimmune liver diseases

(virtually all but more prevalent)

pSjS-PBC

pSS-AIH

SSc-PBC

SSc-AIH

RA-AIH

RA-PBC

PM/DM-PBC

PM/DM-AIH

Arena Dig Liv Dis 2012
Smyk AI High 2012
Rigamonti IJR 2011
Mytilinaiou Dig Liv Dis 2009
Smyk Arthr 2012

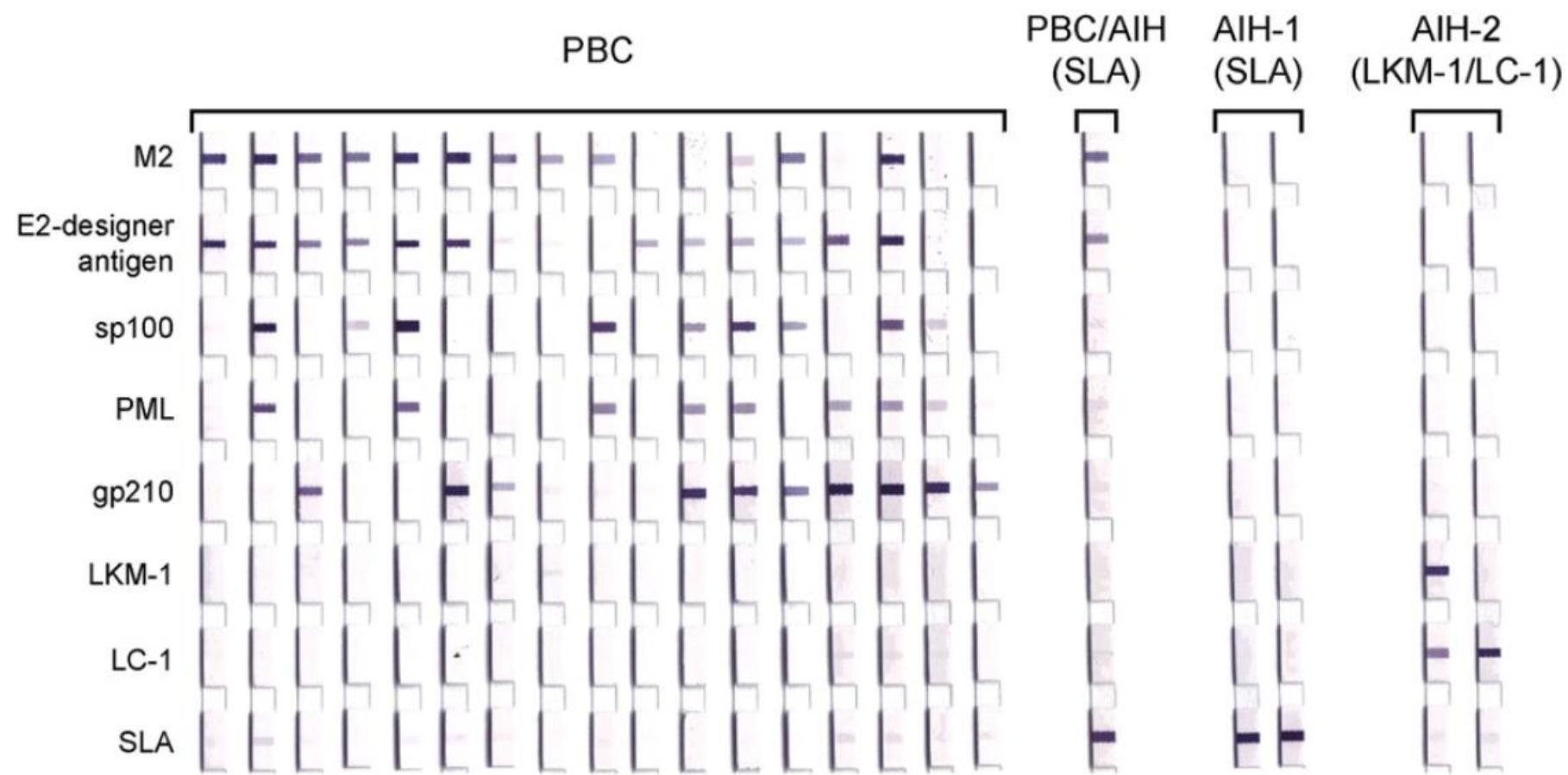


Πρακτικά συμπεράσματα

Practice points

- Monitoring liver function tests is strongly recommended in the management of patients with CTD, especially when the patient is taking DMARDs or drugs that are potentially hepatotoxic;
- Before initiating any immunomodulatory or antiinflammatory treatment patients should be evaluated for the presence of viral hepatitis or liver cirrhosis;
- The presence of chronic hepatitis or liver cirrhosis does not per se increase the risk of idiosyncratic drug reactions;
- When liver function tests are altered in CTD, we recommend to first rule out a drug-induced liver injury, second to evaluate the possibility of a CTD flare or the re-activation of previous HBV or HCV infections, and finally to investigate a coexisting autoimmune liver disease.
- Coexisting autoimmune liver diseases must be evaluated with serum AMA, ANA, and liver ultrasonography while a liver biopsy should be performed only in the presence of challenging diagnoses.





Πρακτικά συμπεράσματα

Practice points

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Grant Giving Bodies



CIMI Laboratory group (Bogdanos lab)



Dept of Rheumatology and Clinical Immunology Physicians



www.autorheumatology.com

University of Thessaly Medical School



Thank you

RA and liver abnormalities

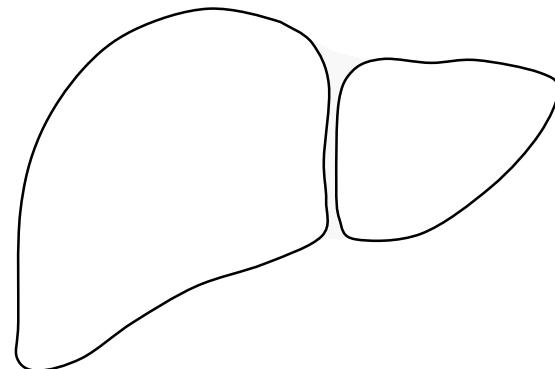
- Abnormal liver tests, mainly alkaline phosphatase (ALP) and γGT have been reported in up to 50% of RA cases
- Heterogeneity among studies- Incidence??
- Differential diagnosis prompts exclusion of the following:
 - Liver diseases (autoimmune liver diseases, exacerbation of viral hepatitis)
 - Hepatotoxicity related to treatment prescribed for RA

Smyk Arthr 2012; Kendall Ann Rheum Dis. 1970, Selmi Arth Res Therapy 2011



Liver Involvement in Rheumatoid Arthritis

- RA and abnormal liver function tests
 - ▶ RA and autoimmune liver diseases
 - ▶ RA and hepatotoxicity due to agents administered for the treatment of the disease
 - ▶ RA and reactivation of HBV and HCV in the context of immunosuppressive agents



RA and liver abnormalities

- Prospective study of 31 RA patients with clinical and/or biochemical evidence of hepatic dysfunction with liver biopsy
- 4/31 (13%) definable chronic liver disease
- 27/31 (87%) normal hepatic histology or non-specific reactive changes
- Hepatic abnormality in rheumatoid arthritis remains functional and unexplained

Mills Scott Med J 1980



PA and liver abnormalities

Retrospective evaluations of autopsy material in RA patients not treated with MTX

Recorded final autopsy diagnoses for 182 cases of rheumatoid arthritis

Reported hepatic histology	No. of cases*
Normal liver parenchyma	15
Congestion	112
Fatty change	42
Portal tract inflammation	30
Fibrosis	21
Tumour	15
Amyloid	9
Cirrhosis	5
Vasculitis	3
Cholangitis	2
Viral hepatitis	2
Other infections	3

*In some autopsies, more than one finding was described.

Mean age of death : 65.7 years (24-90)
Mean disease duration: 16.1 years (1-53)

Ruderman Br J Rheumatol 1995



PA and liver abnormalities

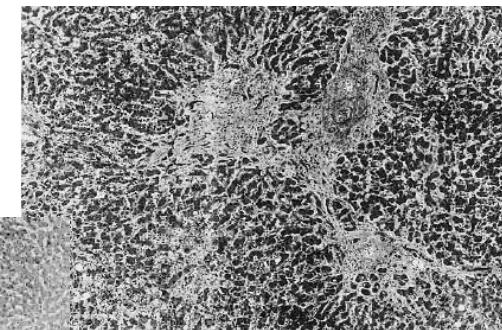
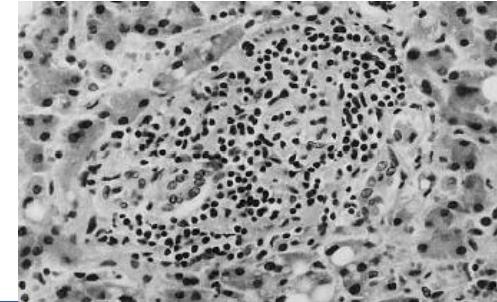
Retrospective examination of liver biopsies from autopsy material

Portal tract inflammation and fibrosis seen on blinded pathological review of 90 normal and abnormal autopsy cases

	Histologic grade				
	0	1	2	3	4
Abnormal autopsy cases (66)					
Portal tract inflammation	14	44	6	–	2
Diffuse fibrosis	48	8	3	1	1
Fibrosis with identifiable cause	–	2	1	2	–
Normal autopsy cases (24)					
Portal tract inflammation	13	11	–	–	–
Diffuse fibrosis	22	2	–	–	–

52/66 (78%)

14/66 (21%)



cirrhosis: 1%

No clinical information for these patients to rule out the possibility that other medications or concurrent illnesses may have contributed to hepatic pathology

Ruderman Br J Rheumatol 1995



Αυτοάνοσες Ρευματικές Παθήσεις που προσβάλουν το Ήπαρ

(σχεδόν όλες αλλά πιο συχνά)

1. Systemic lupus erythematosus
2. Antiphospholipd syndrome
3. Systemic sclerosis
4. pSjögren's syndrome
5. Inflammatory myopathies



Autoimmune hepatitis induced by anti-TNF agents

- Cases of autoimmune hepatitis (AIH) are rare, representing less than 2% of all autoimmune processes related to anti-TNF agents

Ramos-Casals Autoimmun Rev 2010

- Most patients responded completely to anti-TNF withdrawal
- The majority of cases need immunosuppression to treat the disease (prednisolone+AZA/or MMF) with a rapid response to treatment, achieving complete remission in 2 months

Efe Autoimmun Rev 2013

Liver Injury From Tumor Necrosis Factor- α Antagonists: Analysis of Thirty-four Cases

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2013;11:558–564

Infliximab more common

Acute hepatocellular injury >75%

Median time=13weeks

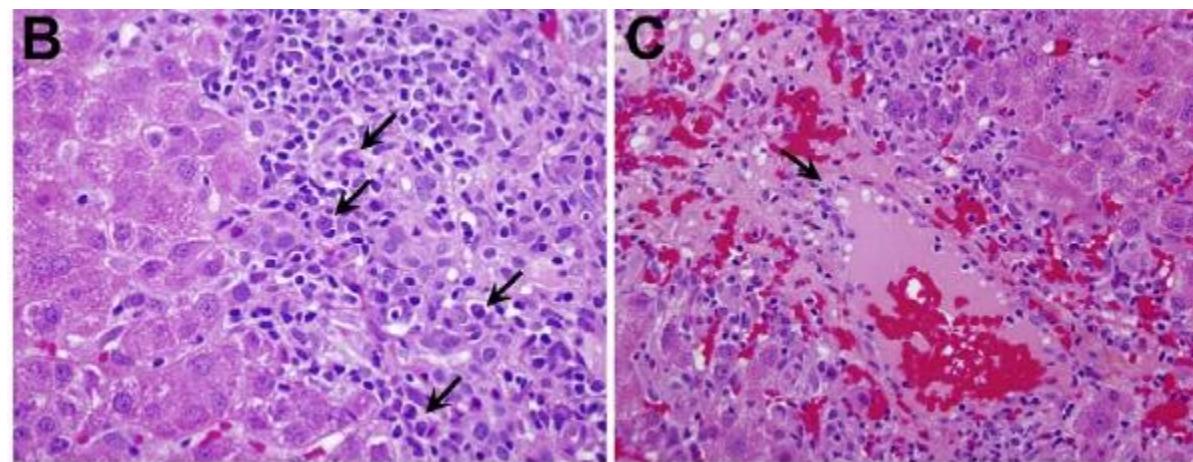
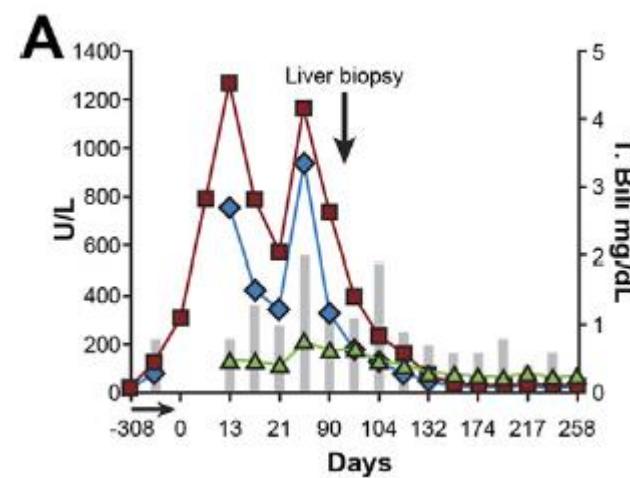
Autoimmune features (ANA/SMA+)

Histology suggesting AIH

Anti-TNF- α agent and DILIN case number or reference citation	Age (y), sex	Disease	Dose	Duration of therapy before onset of DILI (wks)
Infliximab DILIN 1	28, M	CD	5 mg/kg	20
Infliximab DILIN 2	54, F	PsA	5 mg/kg	12
Infliximab DILIN 3	35, F	CUC	5 mg/kg	2
Etanercept DILIN 4	34, F	Ps	50 mg	15
Etanercept DILIN 5	35, F	Ps	25 mg twice per week	16
Adalimumab DILIN 6	33, F	CD	40 mg	52
Infliximab ⁵	48, M	AS	5 mg/kg	14
Infliximab ⁶	48, M	AS	5 mg/kg	36
Infliximab ¹⁶	46, F	PsA	5 mg/kg	22
Infliximab ²⁸	22, F	Ps	5 mg/kg	6
Infliximab ³²	54, F	AS	5 mg/kg	12
Infliximab ³⁵	33, M	Ps	NA	20
Infliximab ³⁶	38, F	RA	3 mg/kg	38
Infliximab ³⁷	43, F	CD	5 mg/kg	4
Infliximab ³⁸	40, F	PsA	5 mg/kg	22
Infliximab ²³	64, M	Ps	5 mg/kg	3
Infliximab ³⁰	53, F	PsA	3 mg/kg	30
Infliximab ³³	36, F	RA	3 mg/kg	12
Infliximab ³⁹	34, F	CUC	5 mg/kg every 2 weeks	16
Infliximab ⁴⁰	28, M	CUC	5 mg/kg	1.5
Infliximab ¹⁴	39, F	RA	3 mg/kg	32
Infliximab, case 1 ⁴¹	37, M	Ps	5 mg/kg	12
Infliximab, case 2 ⁴¹	51, M	Ps	5 mg/kg	10
Infliximab ⁴²	60, M	CD	5 mg/kg	14
Infliximab ¹⁹	46, M	CD	5 mg/kg	6
Infliximab ⁴³	45, F	CD	5 mg/kg	7
Infliximab ⁴⁴	38, F	CD	5–10 mg/kg	104
Infliximab ²⁰	33, M	CD	NA	20
Infliximab ⁴⁵	58, F	CD	5 mg/kg	12
Etanercept ³¹	50, F	RA	25 mg twice per week	2
Etanercept ²⁹	9, F	JIA	0.4 mg/kg twice per week	40
Adalimumab ²⁷	36, F	PsA	40 mg every other week	12
Adalimumab ¹⁵	46, M	PsA	40 mg every other week	12
Adalimumab ²⁶	35, F	RA	NA	5

Liver Injury From Tumor Necrosis Factor- α Antagonists: Analysis of Thirty-four Cases

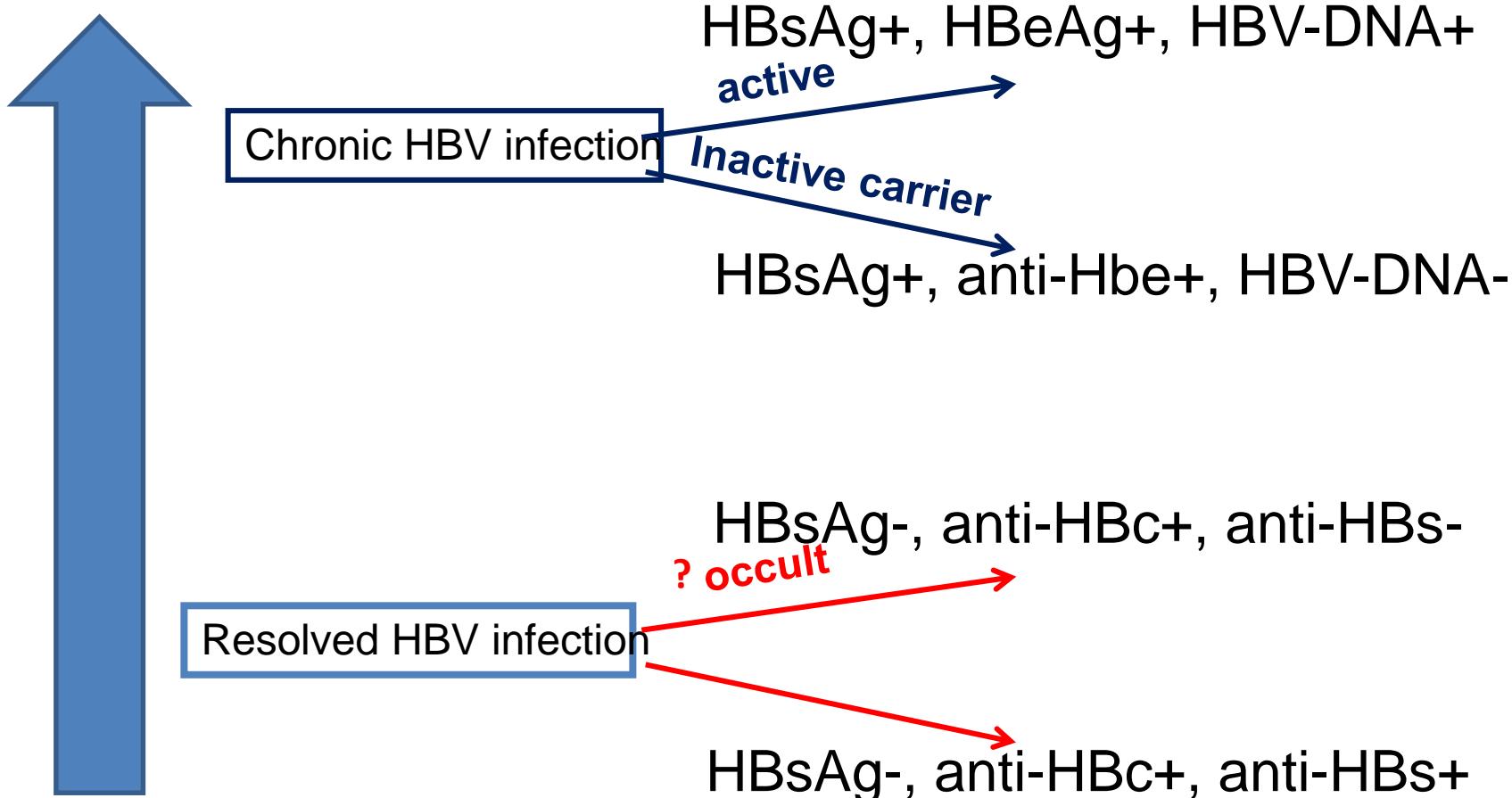
CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2013;11:558-564



Ηπατική δυσλειτουργία στα πλαίσια PA και επανεργοποίησης HBV και HCV υπό¹ ανοσοκατασταλτική αγωγή



The risk of HBV reactivation depends on the phase of the natural history of the disease



Immunosuppressants/ immunomodulatory agents associated with HBV reactivation

- Alkylators (cyclophosphamide, chlorambucil)
 - Antimetabolites (cytarabine, 5-FU, gemtuzumab, 6-MP, methotrexate)
 - Antitumor antibiotics (anthracyclines, bleomycin, mitomycin C)
 - Plant alkaloids (vincristine, vinblastine)
 - Corticosteroids
 - Fludarabine
 - Anti-CD20 (Rituximab)
 - Anti-CD52 (Alemtuzumab)
-
- Anti-TNF (Infliximab, Adalimumab, Etanercept, Certolizumab)



Prevention of HBV reactivation

- All candidates for chemotherapy and immunosuppressive therapy should be screened for HBsAg and anti-HBc prior to initiation of treatment (A1).
- Vaccination of HBV seronegative patients is highly recommended (A1).

AASLD Practice Guidelines Hepatology 2009, EASL Clinical Practice Guidelines 2012



