14TH ANNUAL CONFERENCE
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London

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Extra Hepatic Complications of HCV: From Cryoglobulins to Lymphoma

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Extrahepatic Effects of HCV

- Common ‘non-specific’ effects
- Common ‘specific’ effects
- Rare ‘specific’ effects

Extrahepatic Effects of HCV

HEALTH WARNING

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- HCV is common

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- HCV is common
- HCV is diagnosed by doctors

Extrahepatic Effects of HCV

HEALTH WARNING

- HCV is common
- HCV is diagnosed by doctors
- Co-incidences are to be expected

Extrahepatic effects of HCV

Endocrine	Hyperthyroidism [4–6]
	Hypothyroidism [6–8]
	Hashimoto's disease [9,10]
	Thyroid autoantibodies [6,8,11–13]
	Diabetes mellitus [14,15]
Salivary gland and eye	Sialadenitis* [13,16,17]
	Mooren corneal ulcer [18–20]
	Uveitis [21]
Haematological and lymphoid	Mixed cryoglobulinaemia and vasculitis* [22–25]
	Aplastic anaemia [26,27]
	Idiopathic thrombocytopenia [13,28,29]
	Non-Hodgkin's B lymphomas* [30–33]
Kidney, neuromuscular and joints	Glomerulonephritis* [34–36]
	Muscle weakness* [37,38]
	Latent muscular abnormalities [39]
	Peripheral neuropathy* [40]
	Arthritis/arthralgias* [1,41]
	Rheumatoid arthritis* [41,42]
Dermatological	Cutaneous necrotizing vasculitis* [43–45] (Leukocytoclastic vasculitis)
	Porphyria cutanea tarda [46,47]
	Lichen planus [45,48–50]
	Erythema multiforme* [51]
	Erythema nodosum* [52]
	Malacoplakia [53]
	Urticaria* [54]
	Pruritus [55]
Autoimmune and miscellaneous	Polyarteritis nodosa [56–58]
	Pulmonary fibrosis* [59] and pulmonary vasculitis* [60]
	Hypertrophic cardiomyopathy (240)
	CRST syndrome [13]
	Antiphospholipid syndrome [61,62]
	Granulomas [63,64]
	Autoimmune hepatitis type 1 and 2 [65–68]
	Presence of autoantibodies [7,69,70]

*Frequently related to mixed cryoglobulinaemia.

Hadziyannis JVH 2007

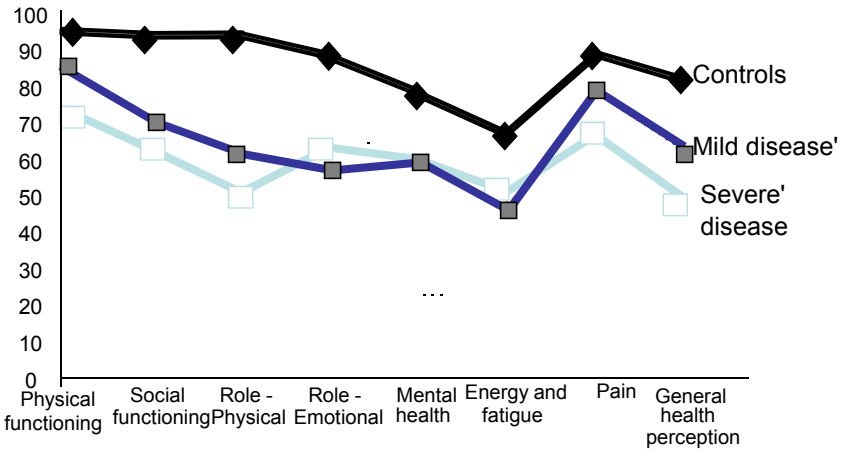
Extrahepatic effects of HCV

- Not every reported effect is causal

Extrahepatic Effects of HCV

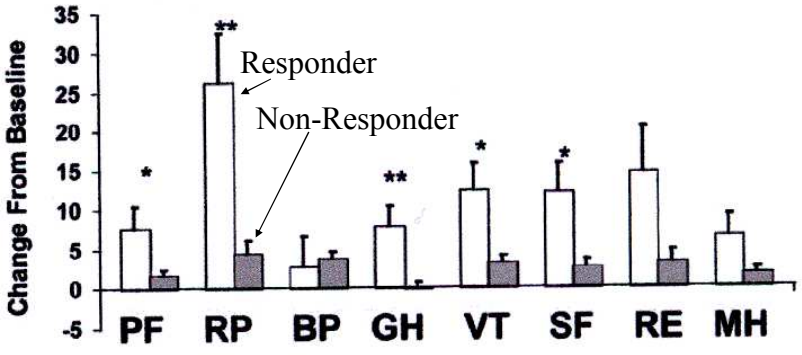
- Common ‘non-specific’ effects
- Common ‘specific’ effects
- Rare ‘specific’ effects

Patients with chronic HCV feel unwell



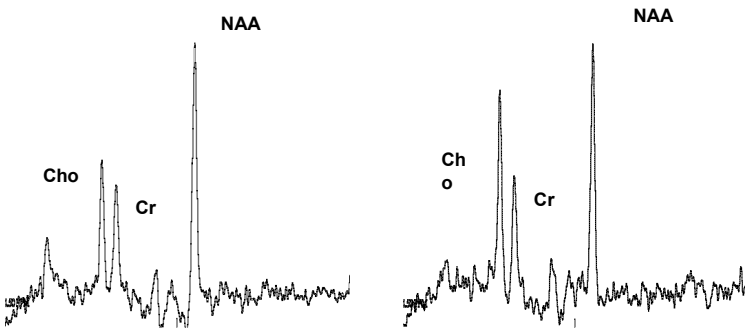
Foster et al Hepatology 1998

Non-specific malaise is 'cured' by viral eradication



Bonkovsky Hepatology 1999

Does Hepatitis C Infect the Brain ?
Magnetic Resonance Spectroscopy Results



Forton et al Lancet 2002

HCV and malaise

- Many HCV infected patients complain of non-specific fatigue, ‘brain fog’, etc
- The symptoms often improve with therapy
- The mechanism is unknown but the brain may be directly involved

Extrahepatic Effects of HCV

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- Common ‘specific’ effects
- Rare ‘specific’ effects

Extrahepatic Effects of HCV

- Diabetes
- Thyroid dysfunction
- Positive autoantibodies

Diabetes and HCV

- Diabetes is common in patients with HCV (RR of around 2)
- Diabetes is common in co-infected patients with HCV

Risk factors for diabetes mellitus and early insulin resistance in chronic hepatitis C J Hepatol 2001

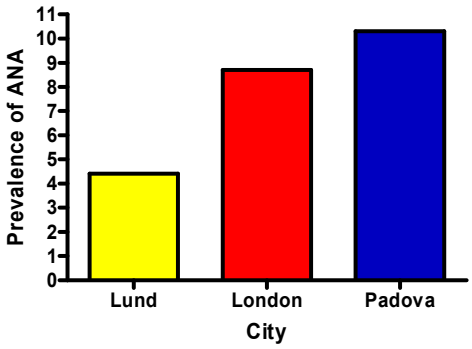
Hepatitis C is associated with type 2 diabetes mellitus in HIV-infected persons without traditional risk factors HIV Medicine 2007

Thyroid Dysfunction and HCV

- Common –

  ? 1-2% of patients have thyroid dysfunction
- May be exacerbated by therapy

Positive autoantibodies - geographical differences



Thursz et al J Viral Hep 2004:459-64

Other specific effects

- A variety of autoimmune disorders have been associated with HCV
- These include lichen planus, dry eyes etc, etc

Dry Eyes and HCV

	HBV 10	HCV 25
McMonnies score >13	1 (10)	0
Blepharitis	2 (20)	7 (28)
Tear debris	4 (40)	3 (12)
Tear film meniscus ≤ 0.5mm	0	0
Fluoroscein breakup time ≤10s	4(40)	11(44)
Rose bengal stain (van B score) ≥3.5	1 (10)	0

HCV does NOT cause dry eyes

Extrahepatic Effects of HCV

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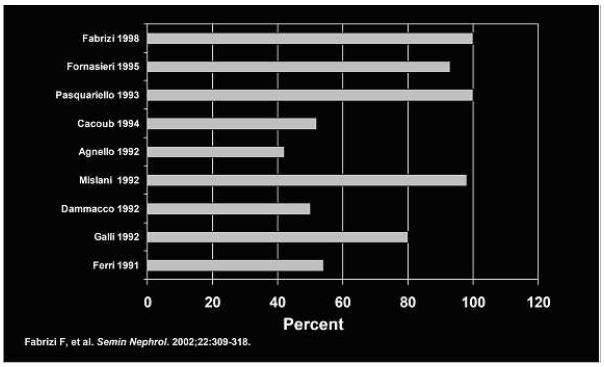
Incidence of HCV in Cryoglobulinaemia



Cryoglobulins and HCV

- HCV is associated with type II and type III cryoglobulins

  (Type II monoclonal + polyclonal, type III polyclonal)

Cryoglobulins and HCV

- Who gets them
- What they do
- How they are formed
- What can we do about them

Cryoglobulins and HCV

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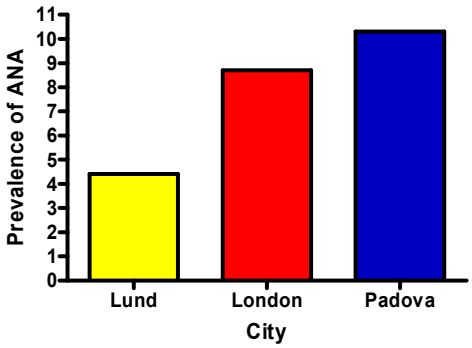
Cryoglobulins and HCV

- Some studies suggest that up to 50% of patients with HCV have cryoglobulins

But…..

Autoimmune disorders in HCV are geographical



Thursz et al J Viral Hep 2004:459-64

Cryoglobulins and HCV

- Some studies suggest that up to 50% of patients with HCV have cryoglobulins

But…..

- Most studies are based on Italian patients who have a high prevalence of autoimmunity associated with HCV

Cryoglobulins and HCV

- Who gets them
- What they do
- How they are formed
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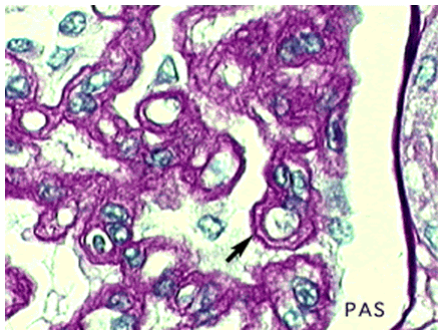
Cryoglobulins and HCV

- Symptoms range from zero to full blown cryoglobulinaemia with end organ damage
- Skin, peripheral nerves and kidneys usually involved

Membranoproliferative GMN and cryoglobulins



Cryoglobulins and skin lesions

Cryoglobulins and HCV

- Who gets them
- What they do
- How they are formed
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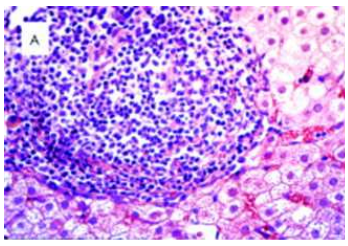
Cryoglobulins and HCV Pathogenesis

FACTS

1. HCV is often associated with high globulin fractions
2. HCV is often associated with lymphoproliferation
3. HCV may be associated with cryoglobulins
4. HCV may be associated with B cell lymphoma

HCV is associated with lymphoproliferation



HCV associated lymphoproliferation

- Lymphoid infiltrates in HCV are oligoclonal

(Magalini et al J Pathol 1998;185:86-90)

- BCL-2 translocations (t(14-18)) are common in patients with HCV (26%) and HCV associated cryos (71%)

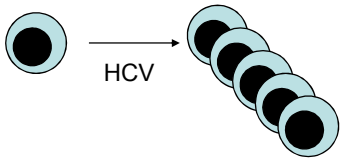
(Zignego et al Hepatology 2000;31:474-79)

HCV associated lymphoproliferation

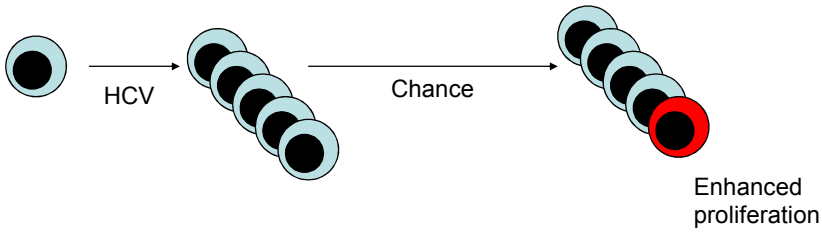
- HCV Envelope protein binds to CD81
- Binding of HCV to CD81 reduces the threshold for B cell activation and increases the frequency of VDJ recombination

(Pileri at al Science 1998;282:938-41)

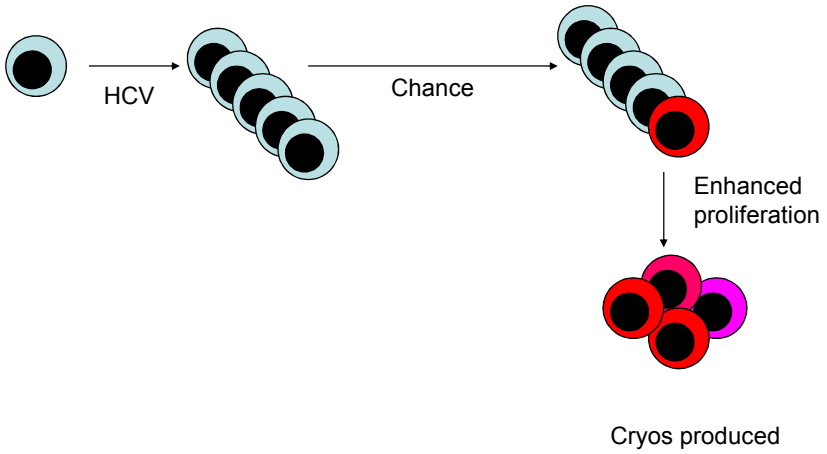
HCV associated lymphoproliferation



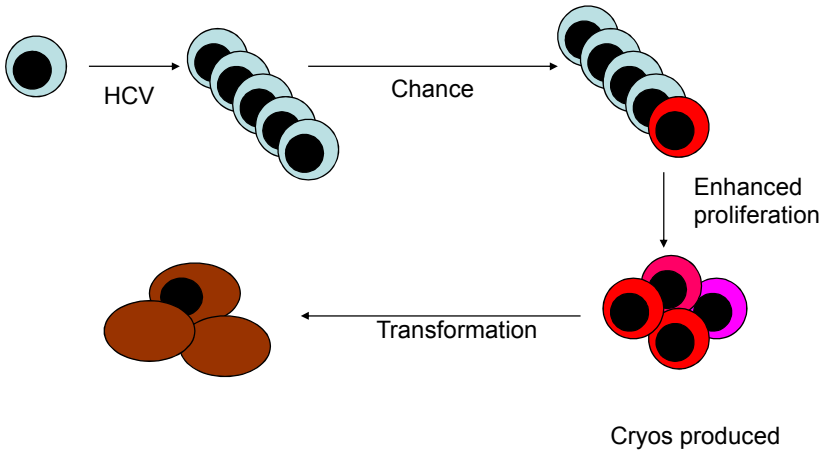
HCV associated lymphoproliferation



HCV associated lymphoproliferation



HCV associated lymphoproliferation



Cryoglobulins and HCV

- Who gets them
- What they do
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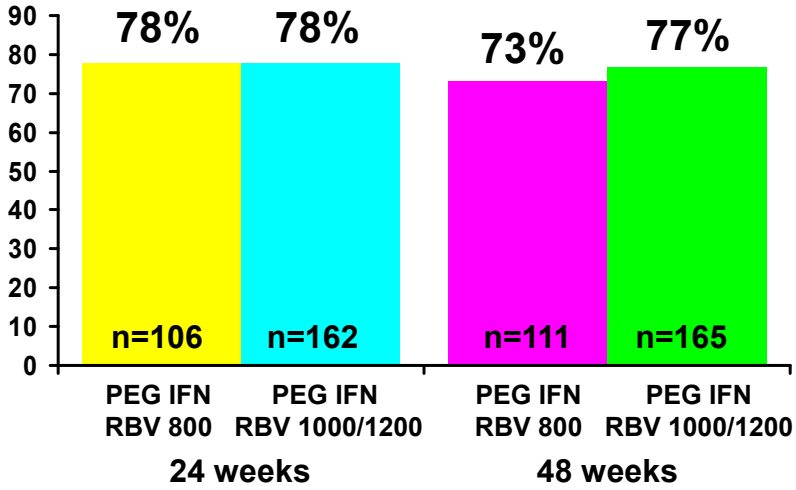
- What can we do about them

Cryoglobulins and HCV Therapy

- If you get rid of the virus the cryos go away

Sustained Response Rates in HCV
Genotype non 1 – 40 KD PEG IFNα2a + Ribavirin



Hadziyannis et al Ann Intern Med 2004:140;346-355

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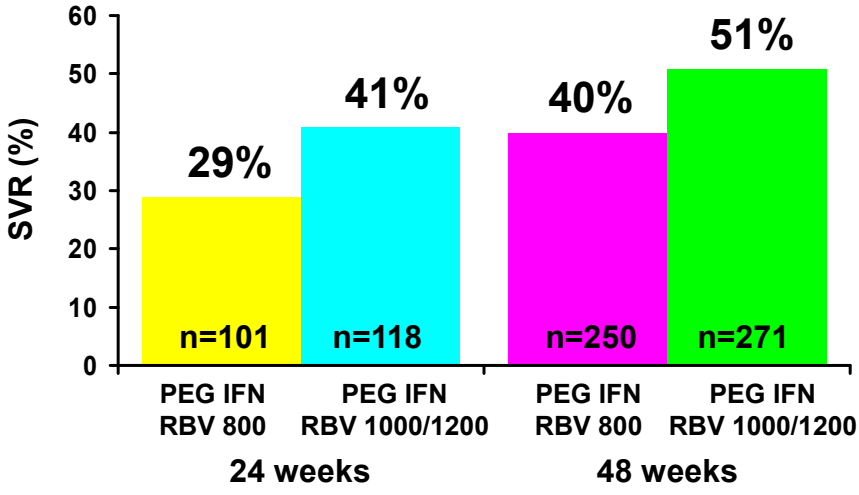

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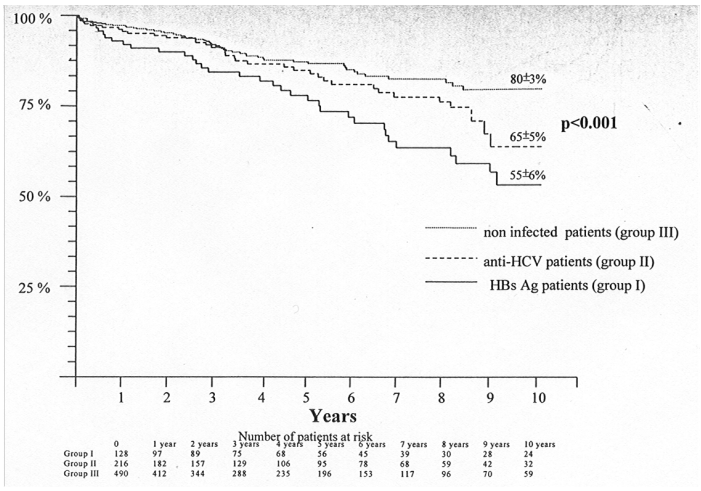
Cryoglobulins and HCV Therapy

- The literature tells us that cryo patients respond like all other patients
- (Not in my clinic they don't!)

Cryoglobulins and HCV Therapy – options for viral failure

1. Cross fingers
2. Long term IFN
3. Immunosuppression
4. Anti-CD20

HCV outcome in renal grafts: Survival



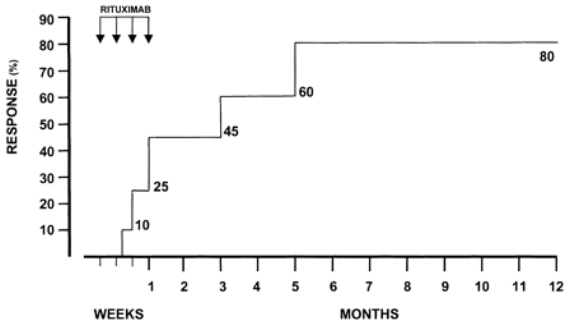
Mathurin et al Hepatology 1999;29:257

Cryoglobulins and HCV Therapy – options for viral failure

- Long term immunosuppression is a poor option
- Anti-CD20 is the current flavour of the month

Anti-CD20 for HCV associated cryoglobulinaemia

N=20



Probability of complete response during rituximab therapy
(12/16 maintained response)

Sansonno et al Blood 2003

Anti-CD20 for HCV associated cryoglobulinaemia

- Pre therapy HCV RNA (responders – 16)
  477,231 IU/ml

- Post rituximab HCV RNA
  765,667 IU/ml

Sansonno et al Blood 2003

Cryoglobulins and HCV

- Clinically significant cryos are rare in UK patients
- The mechanisms of induction of cryos are unclear but may provide clues to other proliferative disorders
- Therapy is uncertain but viral eradication remains the option of choice

Extrahepatic manifestations SUMMARY

- HCV often causes non-specific symptoms
- Specific autoimmune diseases including diabetes and thyroid dysfunction are common
- Symptomatic cryoglublinaemia is a rare and feared complication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