


CHRONIC HCV TREATMENT: In Special Populations.

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Introduction:

- **HCV is the major cause of chronic hepatitis in Egypt. Its end stage is liver cirrhosis with its sequelae as HCC and hepatic failure, which is a major health problem in our country.**
 - **High SVR depends on many factors ,most important one is good patient selection for the standard therapy.**
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**CURRENT STANDARD
THERAPY:**

PEGYLATED INTERFERON

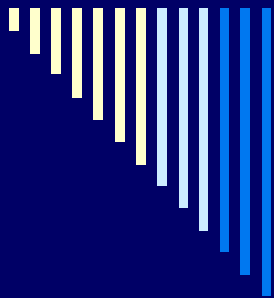
alpha 2 a (40 KD) 180 mcg

alpha 2 b (12 KD) 1.5 mcg/kg
weekly

PLUS

RIBAVIRIN 10.6 mg/kg daily
on divided doses.

For 24- 48 weeks.



- **There is debate about treatment of special populations of HCV infections:**
 - 1) Patients with PNALT.
 - 2) Patients with Liver Cirrhosis
 - 3) HCV with Extra-Hepatic manifestations.
 - 4) HCV with CRF.
 - 5) Co-morbidities: Obesity, DM, thyroid diseases, pregnancy.



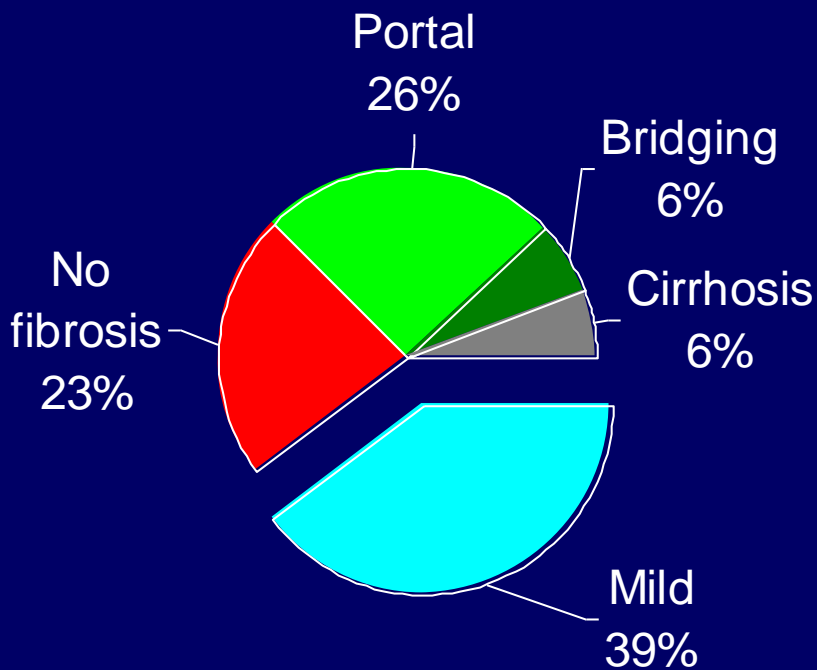
PNALT



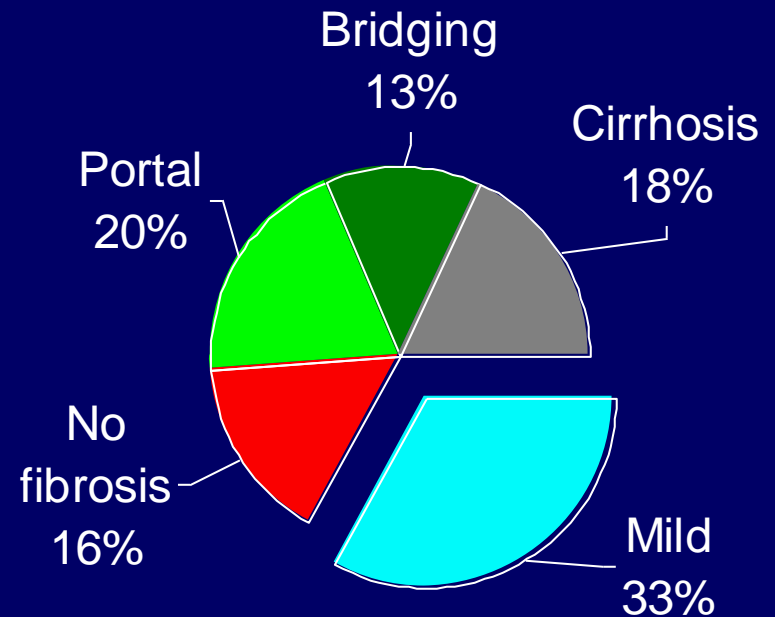
Chronic Hepatitis HCV and Alanine Aminotransferase (ALT)

- **Up to 46% of patients with chronic hepatitis C have ALT levels within the currently defined 'normal' range¹ What is normal ?**
- **Historically excluded from treatment and clinical trials**
 - **Considered 'healthy' or 'asymptomatic'**
 - **Not thought to have progressive fibrosis**
 - **Concern that treatment may cause flares.**
 - **When PNALT?**

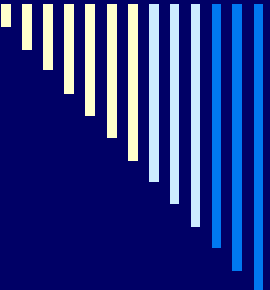
Liver Damage in Chronic HCV Infection: 'Normal' vs Elevated Serum ALT



'NORMAL' ALT



ELEVATED ALT



International, Multicentre, Randomized, Controlled Study for the Treatment of Patients With Chronic Hepatitis C and Persistently Normal ALT Levels With Peginterferon Alfa-2a (40KD) and Ribavirin

**Stefan Zeuzem, Saarland University Hospital, Homburg, Germany;
Moisés Diago, Hospital General de, Valencia, Spain;
Edward Gane, Middlemore Hospital, Auckland, New Zealand;
Rajender Reddy, University of Pennsylvania, Philadelphia;
Paul Pockros, The Scripps Clinic, La Jolla, CA;
Patrizia Farci, Universita di Cagliari, Cagliari, Italy;
Norman Gitlin, Emory University, Atlanta, GA;
François Lamour, Pilar Lardelli, Roche, Basel, Switzerland;
Mitchell Shiffman, VCU Health System, Richmond, VA**

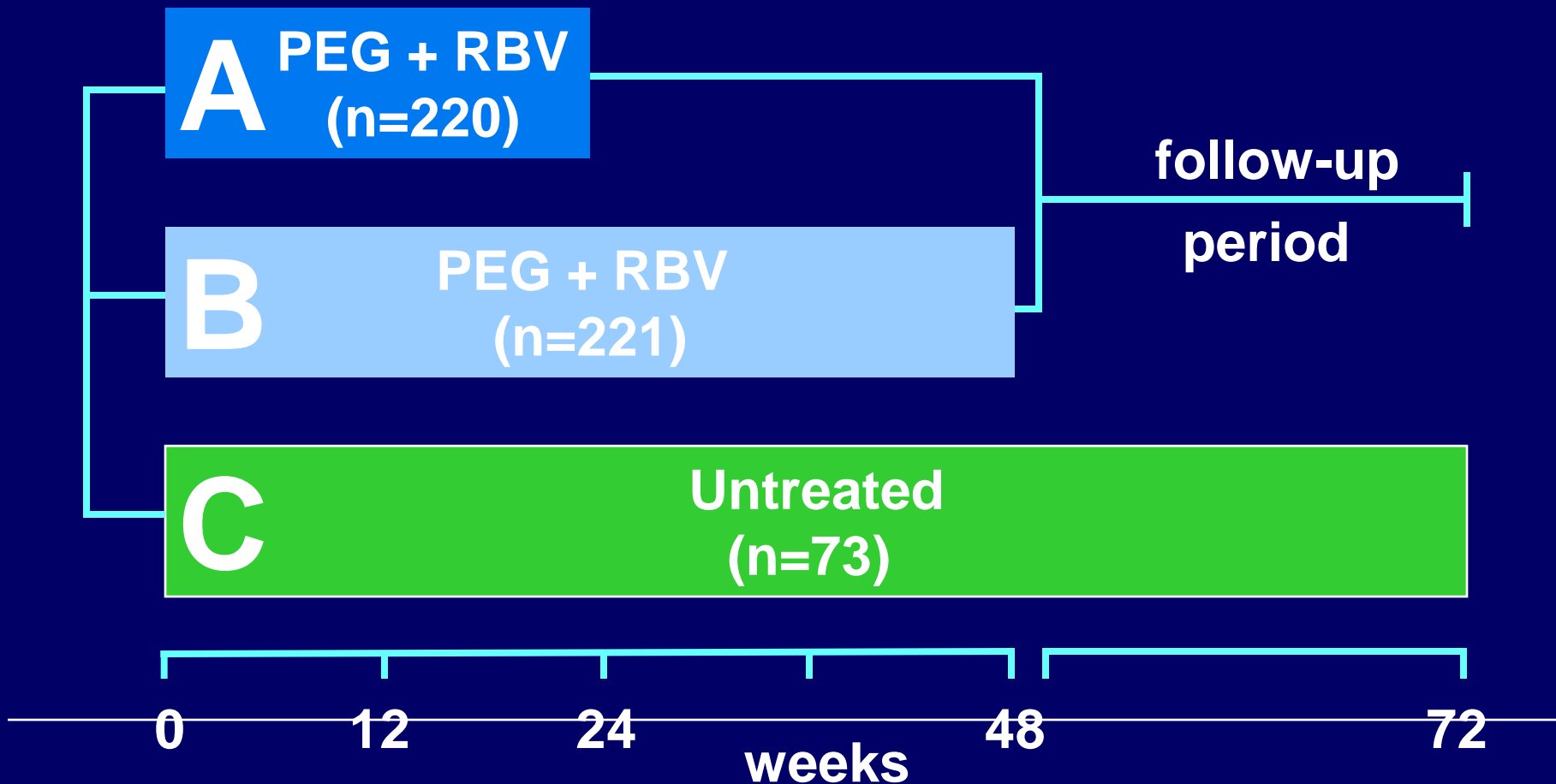


Study Population and Objectives

- **Study population**
 - **Patients with chronic hepatitis C and persistently normal ALT on 3 occasions within 6–18 months before baseline**
 - **Primary**
 - **SVR using Pegylated IFN alpha-2-A (180 µg qw) plus Ribavirin (800 mg/day) for 24 or 48 weeks**
 - **Secondary**
 - **Compare efficacy by HCV genotype**
 - **Monitor serum ALT during and after therapy**
 - **Evaluate safety**
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Study Design

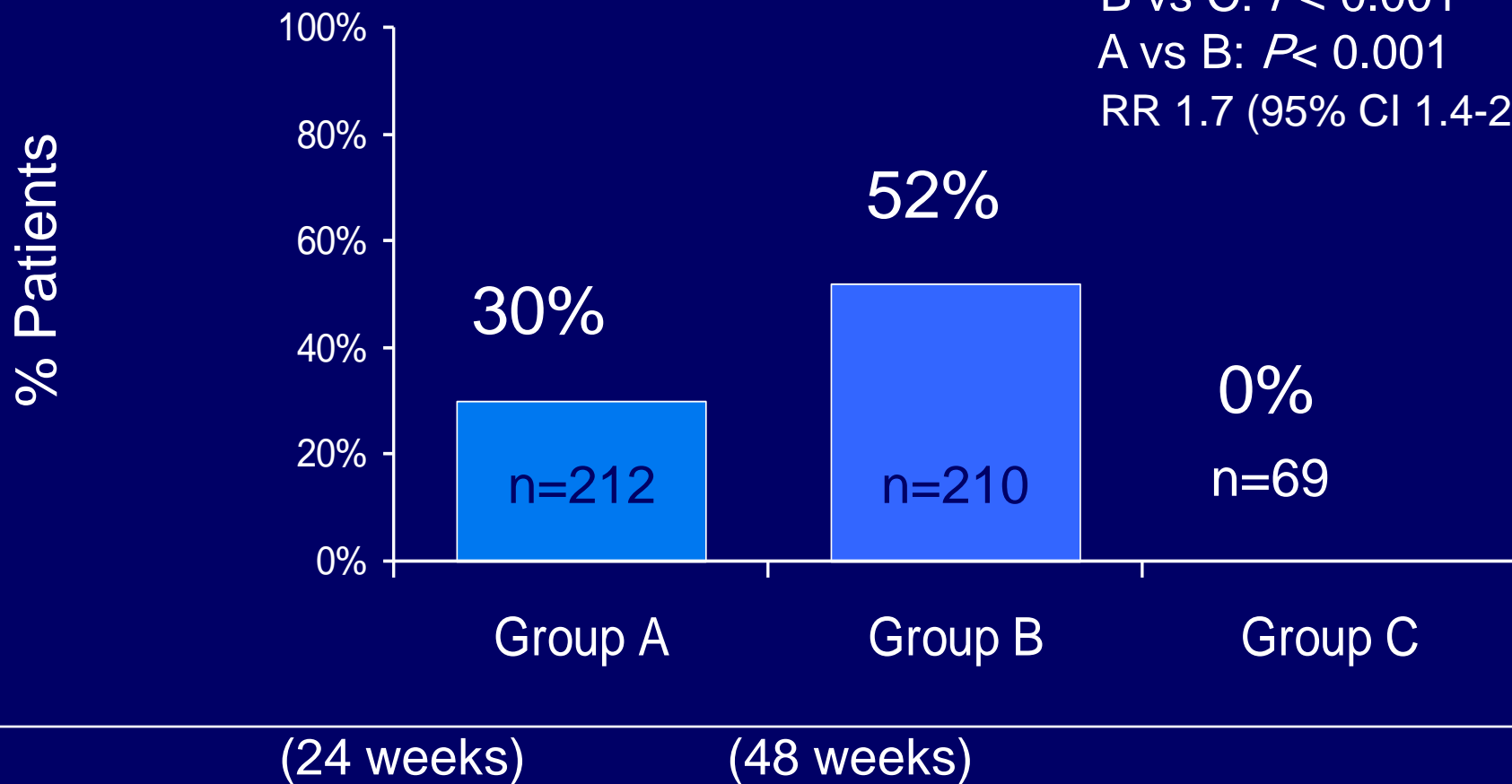
514 patients randomised
(3:3:1)



Sustained Virological Response

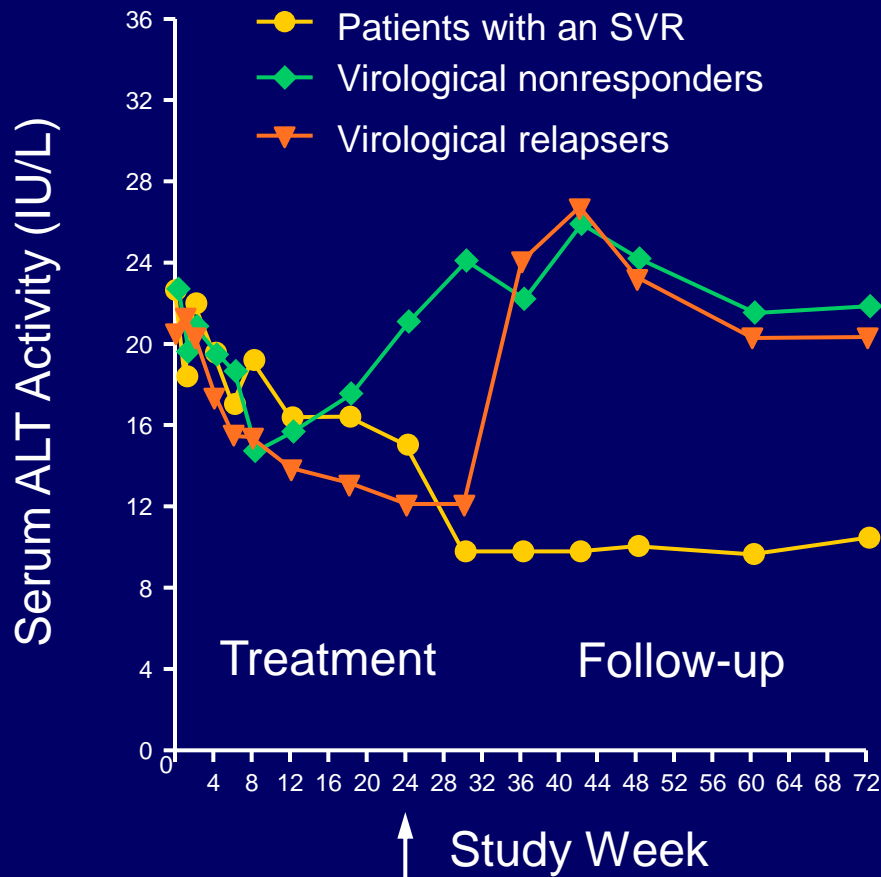
– All Genotypes

A vs C: $P < 0.001$
B vs C: $P < 0.001$
A vs B: $P < 0.001$
RR 1.7 (95% CI 1.4-2.2)

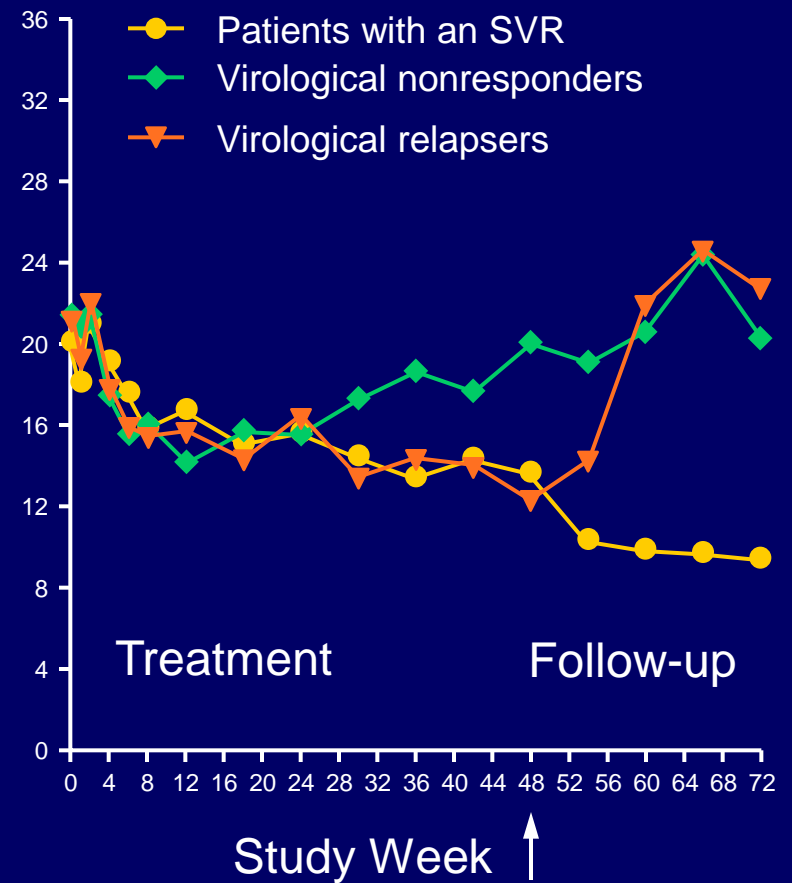


Serum ALT According to Response

Group A (24 weeks)



Group B (48 weeks)



The vertical arrows indicate the end of treatment



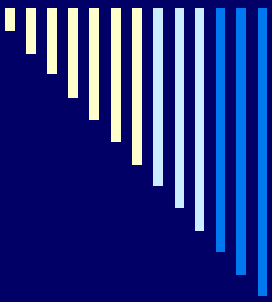
Conclusions:

- Similar efficacy and safety in patients with chronic hepatitis C and elevated or persistently ‘normal’ ALT
 - The genotype-dependent treatment algorithm is also appropriate for patients with PNALT
 - 24 weeks for genotypes 2 or 3
 - 48 weeks for genotype 1&4
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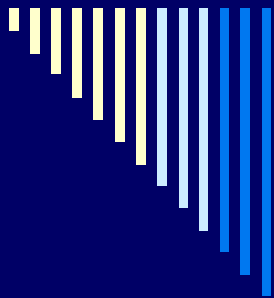


Conclusions:

- **PEGYLATED INTERFERON AND RIBAVIRIN therapy is not associated with flares in ALT.**
 - **Reduction in ALT from a 'normal' level (30 U/L) to a 'healthy' level (10 U/L) was seen in patients with a virological response.**
 - **Since ageing has a negative impact on SVR, a 'watch and wait' strategy may reduce the chance of cure**
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LIVER CIRRHOSIS



- With start of IFN therapy more than 20 years ago, one of the criteria of good selection for treatment was pre-cirrhotic patients.

BUT

Recently, there is an evidence that fibrosis is reversible.



*IFN is a Cytokine which can down regulates
STELLATE CELL.*

- Since more than 10 years there were observation data from Italy that cirrhotic patients received IFN and had SVR , showed marked decrease in F score shown in liver biopsies done after 10 years with even reversal of cirrhosis in some patients.



Four pivotal International RCTs

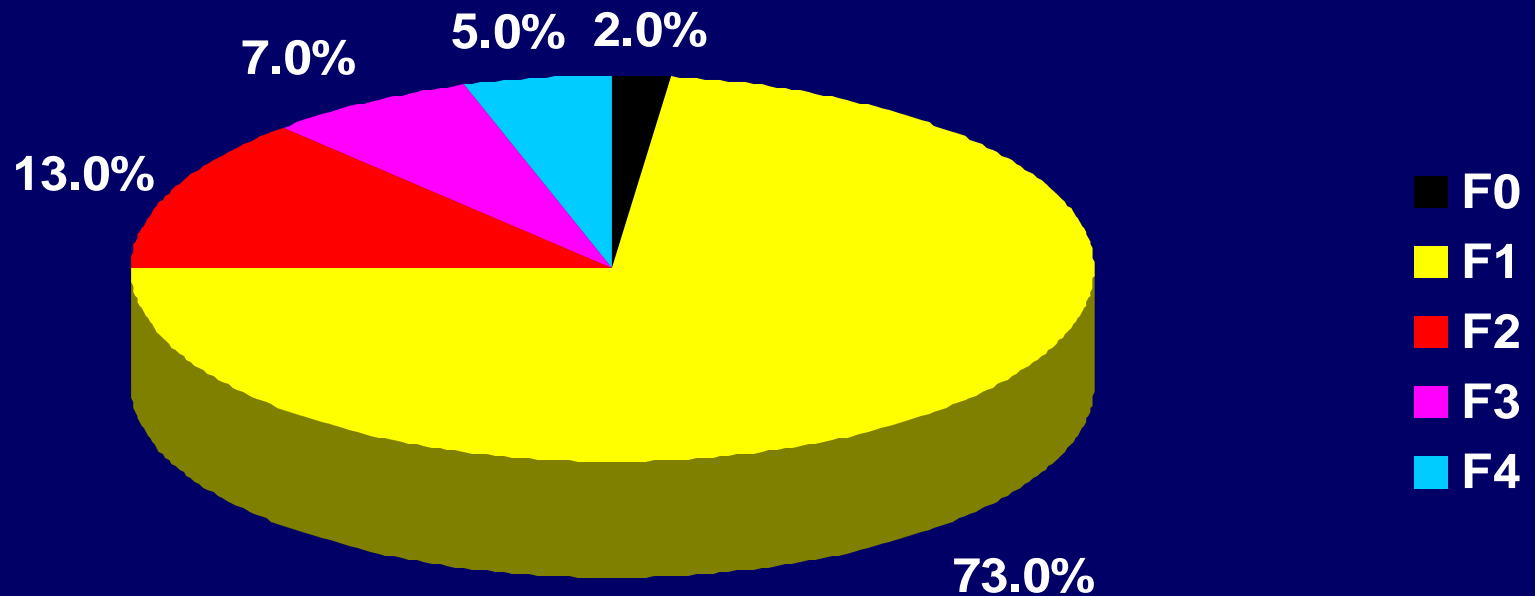
SPRI

Poynard et al, McHutchison et al, Trepo et al,
Manns et al

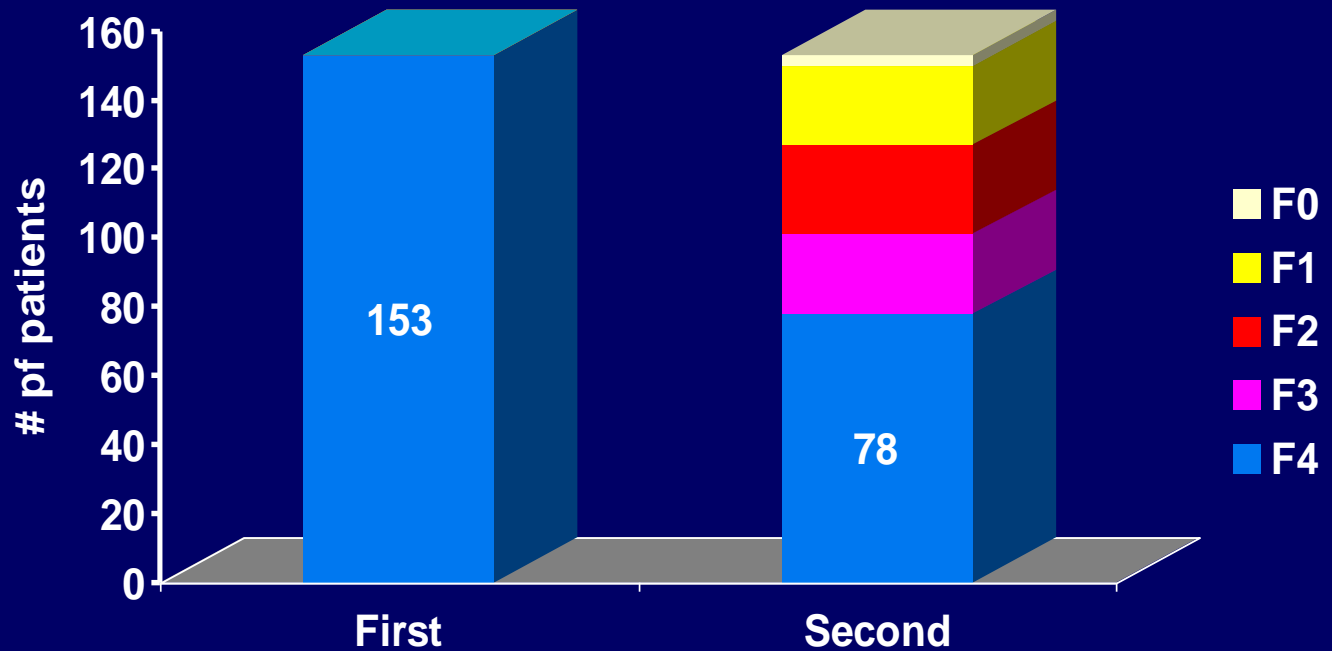
4,493 Patients
4 Trials
Naive HCV patients

3,010 Patients with paired biopsies
One pathologist
One virologist

Characteristics of 3010 included patients



Reversal of cirrhosis in 75 (49%) of patients?





Results

- **Necrosis and inflammation improvement ranged from 39% (interferon 24 weeks) to 73% (optimized PEG 1.5 and ribavirin; $P < 0.001$) .**
- **All regimens significantly reduced the fibrosis progression rates in comparison to rates before treatment .**
- **The reversal of cirrhosis was observed in 75 patients (49%) of 153 patients with baseline cirrhosis.**



Message To Take Home :

- **Pegylated Interferon is safe in compensated cirrhotics and results of SVR in cirrhotics are nearly similar to non-cirrhotics.**
- **Responded cirrhotic patients to combination therapy show regression of fibrosis with elapsing years.**
- **Compensated cirrhotic (Child A) are candidates for Pegylated Interferon therapy hoping for stopping progression of the disease and decreasing risk for HCC, AND EVEN MORE:**

***?? REVERSAL OF
CIRRHOSIS.***



EXTRA-HEPATIC MANIFESTATIONS

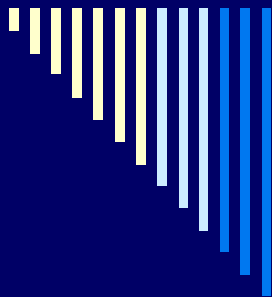
Symptomatic cryoglobulinemia caused by HCV infection is associated with significant morbidity and mortality. Death may result from renal failure or systemic vasculitis. There may also be association with non Hodgkin's lymphoma in patients with cryoglobulinemia. □

One randomized controlled trial of IFN-alfa-2a monotherapy indicated that treatment was effective in eradicating the cryoglobulinemia, improving renal function, and eliminating the symptoms of vasculitis although no beneficial effect on neuropathy is said to occur. □

Post treatment relapse is common and most patients require long term therapy to maintain disease in remission. □



CRF



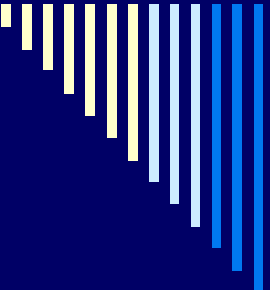
- ❑ **Data support treatment of HCV patients with CRF waiting for renal transplantation.**
- ❑ **Chronic HCV is associated with mixed essential cryoglobulinaemia which increase post-transplantation recurrence of HCV-associated glomerulopathies.**
- ❑ **IFN monotherapy (SVR 33-39%). RBV is associated with severe haemolysis in dialysis patients.**
- ❑ **Relapse rate is very low after transplantation.**
- ❑ **Routine antiviral therapy for patients after kidney transplantation is not recommended because of risk of graft rejection.**



- **Standard IFN therapy---- SVR 27-35%**
- **Recent studies on Pegylated IFN plus low dose RBV 200-800 mg.(wold J Gastroenterology,Janu.2008):**
 - 22 patients, 17 continued treatment and achieved 64% SVR. RBV was monitored by serum level.**
 - Sikole et al,2008: Monotherapy 135 microg PEG-IFN alpha-2a weekly for 48 W. 36% SVR.**



OBESITY

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- **20-37% of HCV patients are obese.**
 - **BMI inversely correlates with SVR**
 - **High Leptin level is a predictor to antiviral treatment resistance.**
 - **Explanation: - fatty liver.
- IR.
- obesity triggered inflammatory reactions ----- decrease response and impairs IFN absorption.**
 - **SO: weight loss + weight-based dosing of IFN and ribavirin in obese patients.**
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PREGNANCY

Ribavirin is teratogenic. □

**IFN-alfa has the potential to damage □
the unborn child.**

**Humans who have reported □
accidental pregnancy during
combination therapy had high fetal
mortality.**

**So, patients and their partners are □
required to avoid pregnancy during
therapy and, in the case of ribavirin,
for 6 months after cessation of
treatment.**



DIABETES MELLITUS

In chronic HCV infection, diabetes was reported as one of the extra hepatic manifestations. □

IFN-alpha seems to be involved in the immunological events that lead to beta-cell destruction and development of type I diabetes. Insulin auto antibodies were positive in 14% of patients treated with IFN for 1 year. □

So, control of diabetes is worsened by IFN-alpha therapy and some patients may become glucose intolerant for the first time during therapy. □

It seems that response rate to IFN is less in diabetics than non-diabetics. Many factors are involved ??? □

(Auto antibodies, fatty liver, tolerability is less and immune system).



THYROID DISEASE

Thyroid abnormalities primarily Hashimoto's disease and, isolated increases of anti-thyroid antibodies (ATOP) are frequent in chronic HCV infection. □

Thyroid dysfunctions occur sufficiently □ often during IFN-alpha therapy(5.5-12.9%) so, it is advisable to monitor TSH every 3 months during therapy(it is sufficient in asymptomatic patients).

Therapy of thyroid dysfunction may be □ required during treatment , often becoming unnecessary once therapy is completed.



Thank You