European Young Hepatologists Workshop

Non-invasive methods for the management of cirrhosis

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Aim of presentation

To evaluate the importance of liver fibrosis in the management of cirrhotic patients.

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One of the leading risk factor of pacients' survival in liver cirrhosis is fibrosis.

- ***Fibrosis*** **is an evolutive process but not irreversible and therefore in some cases can regress.**
- **Liver fibrosis is a dynamic and potentially bidirectional process[1].**

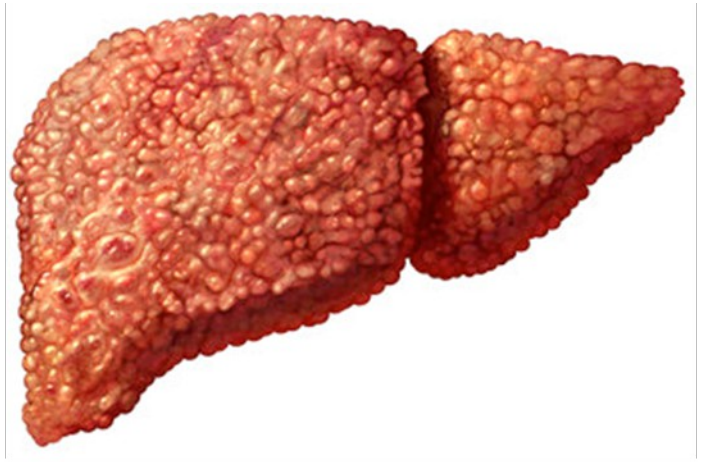
(1)Corresponding author: Antonella Pellicoroapellico@staffmail.ed.ac.uk . Author Affiliations, Centre for Inflammation Research, Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK , *Fibrogenesis & Tissue Repair 2012, 5(Suppl 1):S26 doi:10.1186/1755-1536-5-S1-S26*

Etiology of liver fibrosis

HBV, HCV, HDV

NASH, Cholestasis, Autoimmune disorders

Alcohol, Drugs



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Liver fibrosis evaluation is essential in patients with chronic viral liver disease with major impact on estimation of prognosis, surveillance and treatment decisions[2].

(2)Noninvasive Biomarkers of Liver Fibrosis: An Overview *Hind I. Fallatah. Fellowship of American College of Physicians (FACP) and Arab Board and Saudi Board of Internal Medicine, Medical Department, King AbdulAziz University Hospital, P.O. Box 80215, Jeddah 21589, Saudi Arabia Received 14 October 2013; Revised 11 January 2014; Accepted 27 February 2014; Published 15 April 2014 Academic Editor: Ned Snyder*

✓ **Assessment of liver disease severity is highly recommanded prior to therapy.**

✓ **Identifying patients with cirrhosis or advanced fibrosis if of particular importance, as the post-treatment prognosis depends on the stage of fibrosis[3].**

(3)EASL Recommandations on Treatment of Hepatitis C 2015. J Hepatol (2015), http://dx.doi.org/10.1016/j.jhep.2015.03.025.

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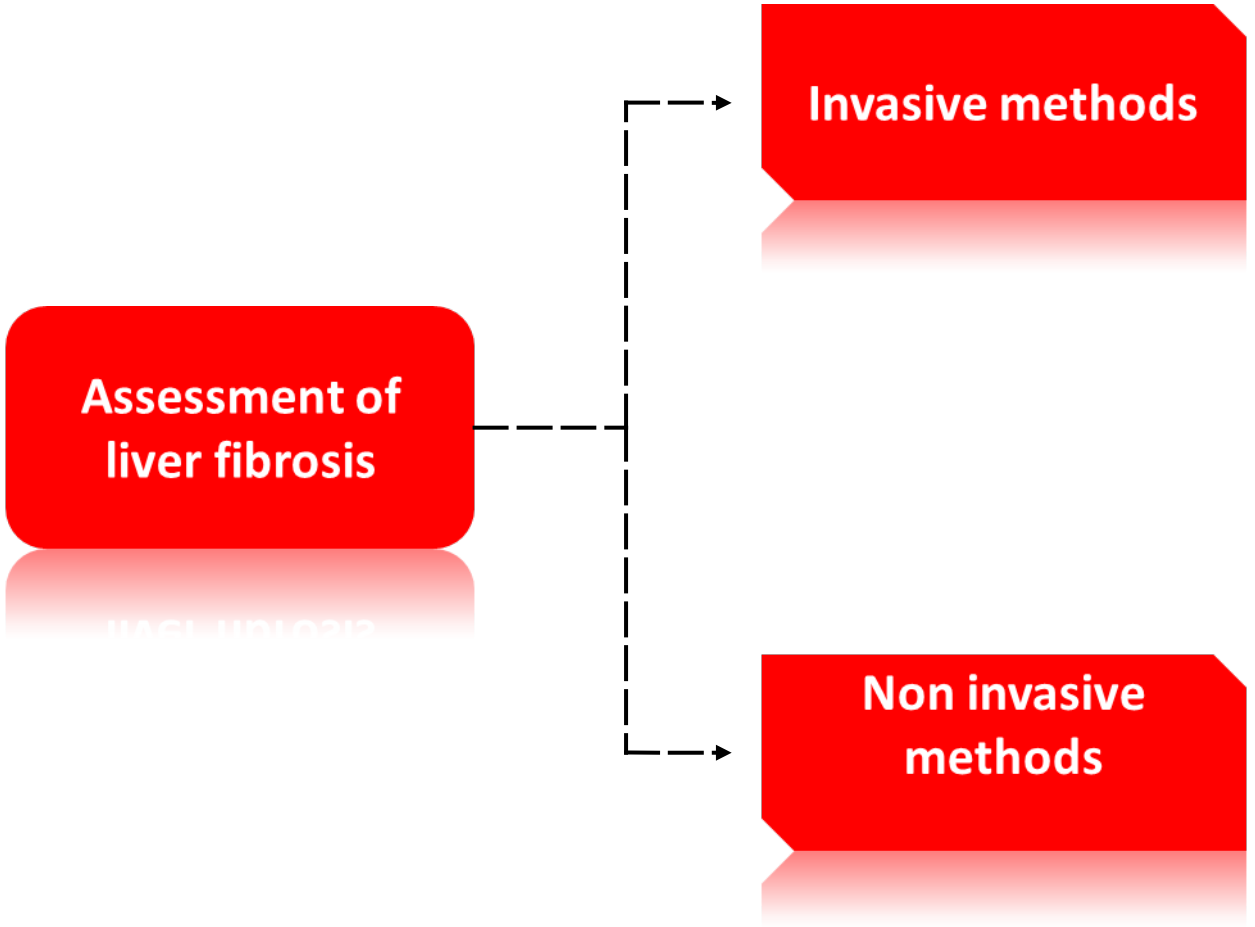
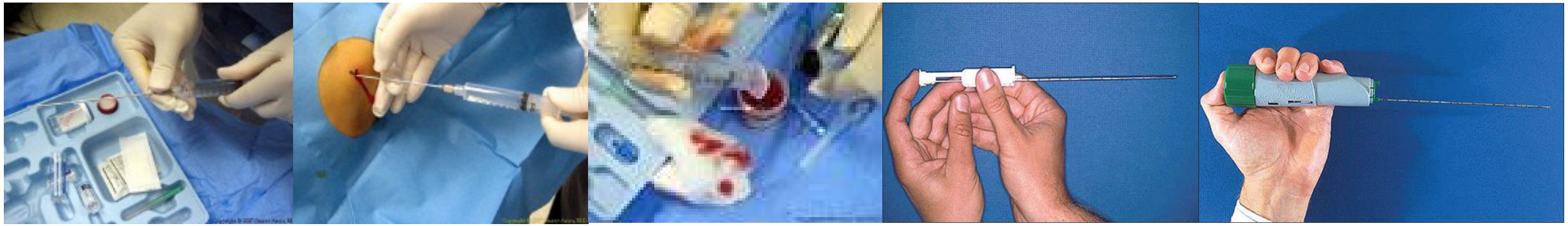
Detection and quantification of hepatic fibrosis is crucial in order to make therapeutic decisions and predict clinical outcomes.



(I) Invazive methods in assessment of liver fibrosis

The "gold – standard" method for liver fibrosis assesment is still considered to be liver biopsy.

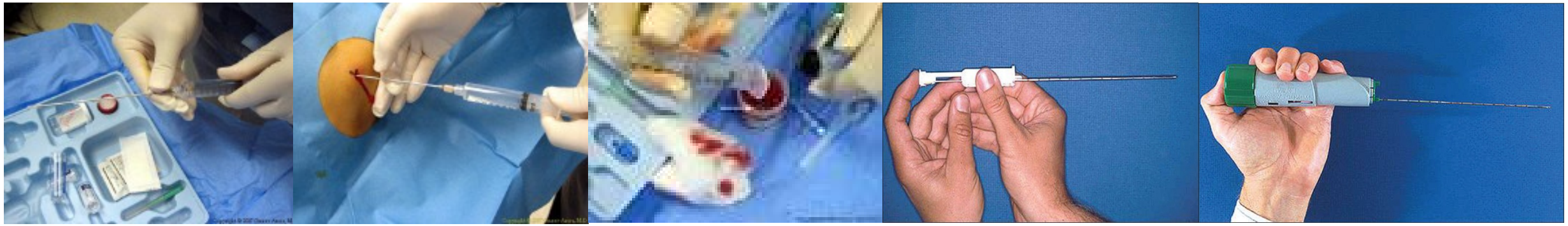
- only 1/50000 of the whole liver tissue is sampled during a liver biopsy.
- to prevent sampling errors it is essential to collect a sufficient amount of tissue.
- making an accurate diagnosis it is important to have one or two samples with lenghts of 15-16cm or longer.
- When to perform liver biopsy? – discordant results at non-invazive methods or if we have steatosis at US and increased ALT



(I) Invazive methods in assessment of liver fibrosis

Risk and complications

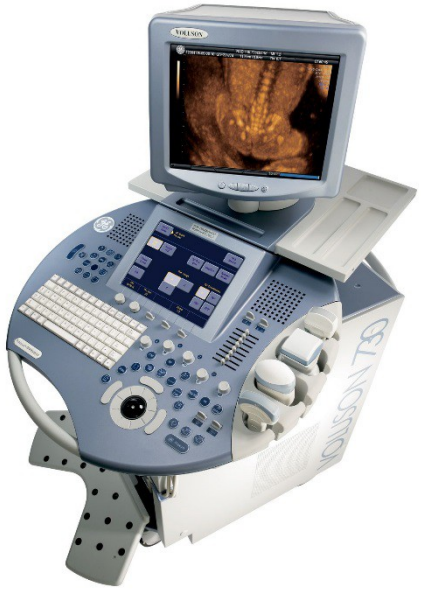
- Pain – 20% or 84% when a mildly unpleasant feeling is included in the assesment.
- The incidence of serious complications and mortality has been reported to be 0,3% - 0,57% and 0,01% respectively[4].



(4)Practices of liver biopsy in France: results of a prospective nationwide survey. For the Group of Epidemiology of the French Association for the Study of the Liver (AFEF).Cadranel JF, Rufat P, Degos F Hepatology. 2000 Sep; 32(3):477-81. (2) Liver biopsy.Bravo AA, Sheth SG, Chopra S N Engl J Med. 2001 Feb 15; 344(7):495-500.

(II) Non - Invazive methods in assessment of liver fibrosis

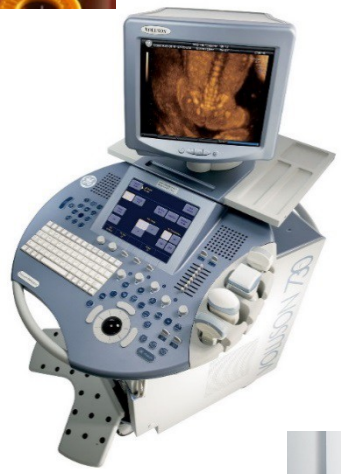
1. Serum markers
(FibroMax, BARD, ELF-panel, APRI, FIB-4, FIBRO-METER, NAFLD Fibrosis Score)



2. Imaging methods
(US, TC, MRI)

3. Elastography
(FibroScan, MRE, ARFI, etc)

(II) Non - Invazive methods in assessment of liver fibrosis



The ideal non-invazive biomarker:

- **Reproductibility**
- **Less/without pain**
- **Simple**
- **High accuracy**
- **High specificity**

(II) Non - Invazive methods in assessment of liver fibrosis

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Internal Medicine Center

Dr. Andreea Radasan

August 2009 – August 2015

FibroScan – 15 700 examinations

Success Rate 100% - 91 %

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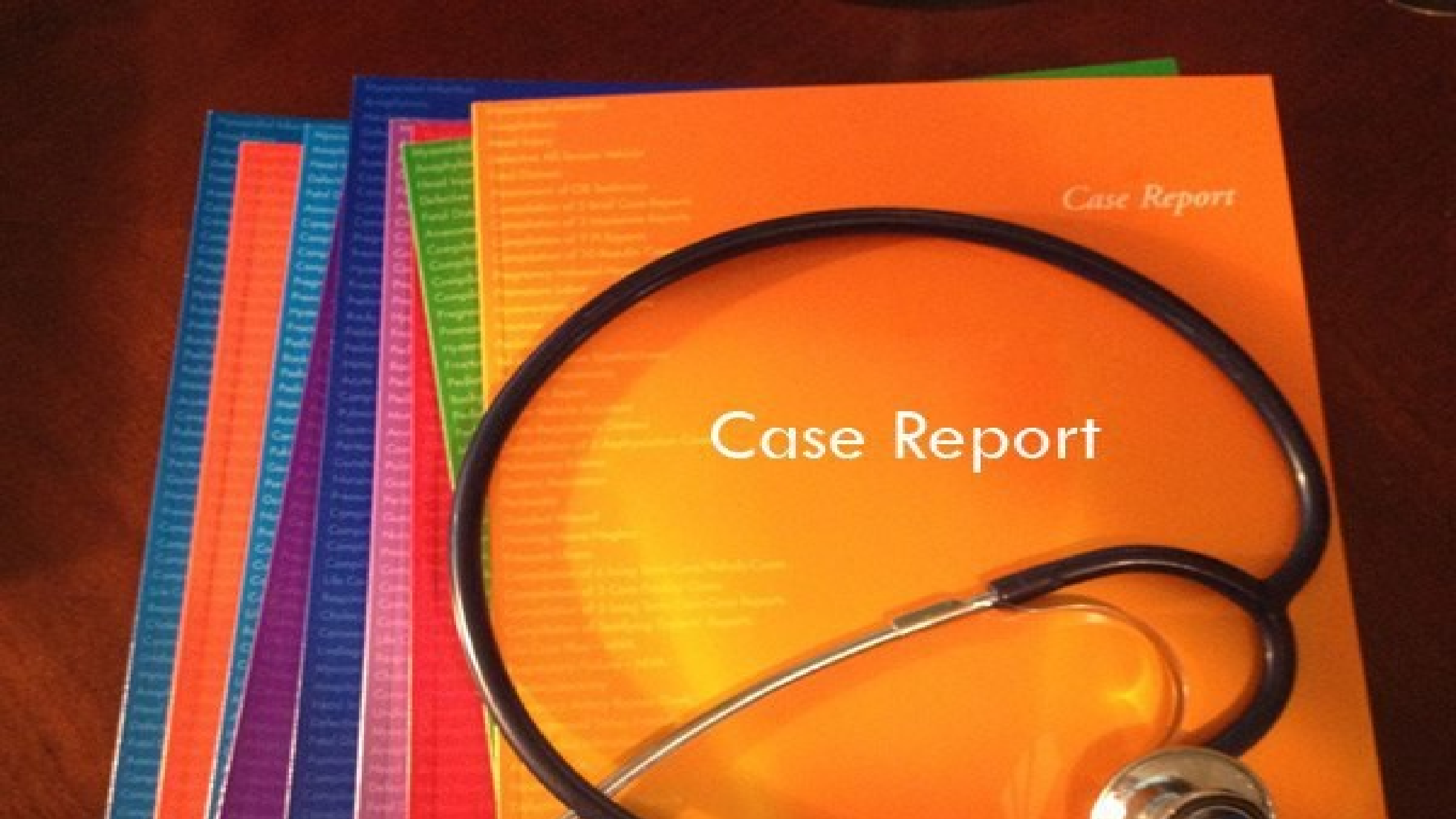

Case Report
Case Report

Case report (I)

- DE, female
- 55 y.o.
- Physics teacher but retired
- BMI = 30,14 Kg/m^2
- No alcohol consumption
- Diabetus Mellitus type 2
- Dyslipidemia
- Wolff–Parkinson–White syndrome

- **HCVchronic hepatitis since 2005**

Case report (II)

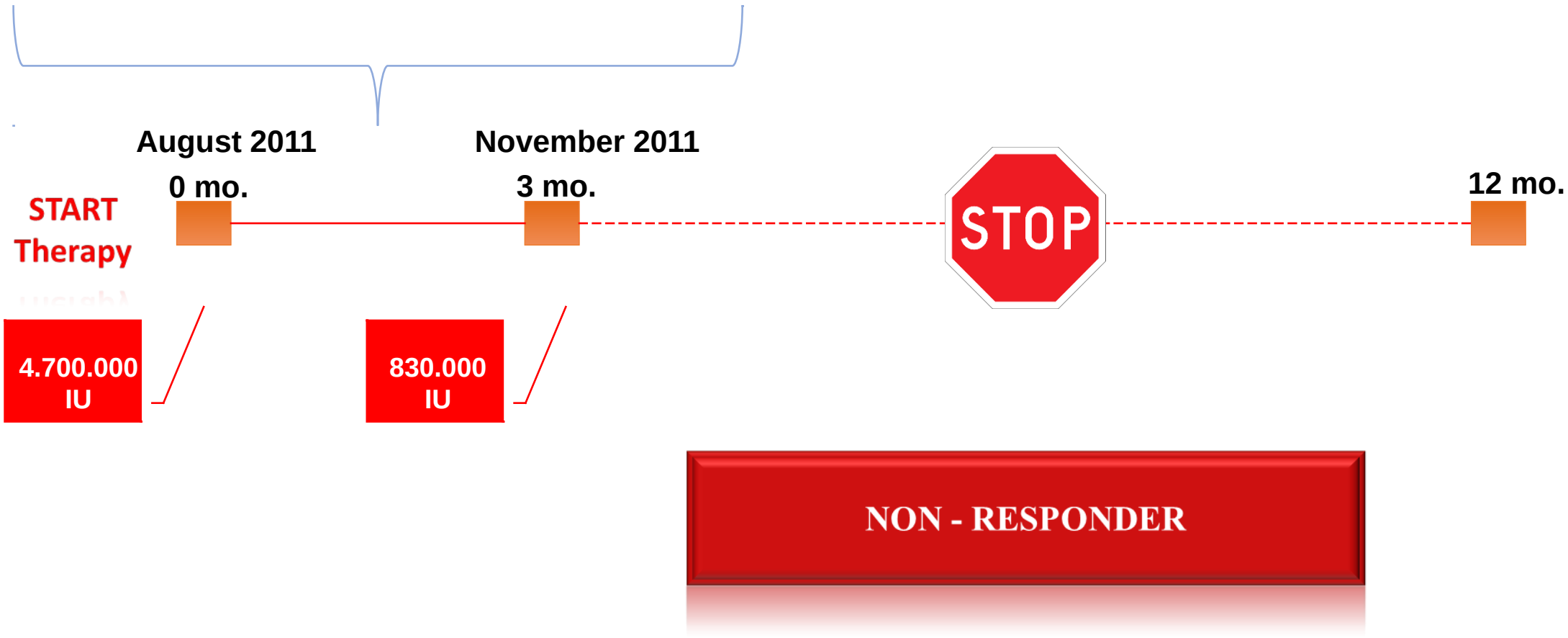
- HCV genotype **1b**
- Interleukin 28b **C/T**

- HCV Viremia

  - *Dec. 2005 – 3.850.000 IU*
  - *Jul. 2009 – 5.152.000 IU*
  - *Aug. 2011 – 4.700.000 IU*

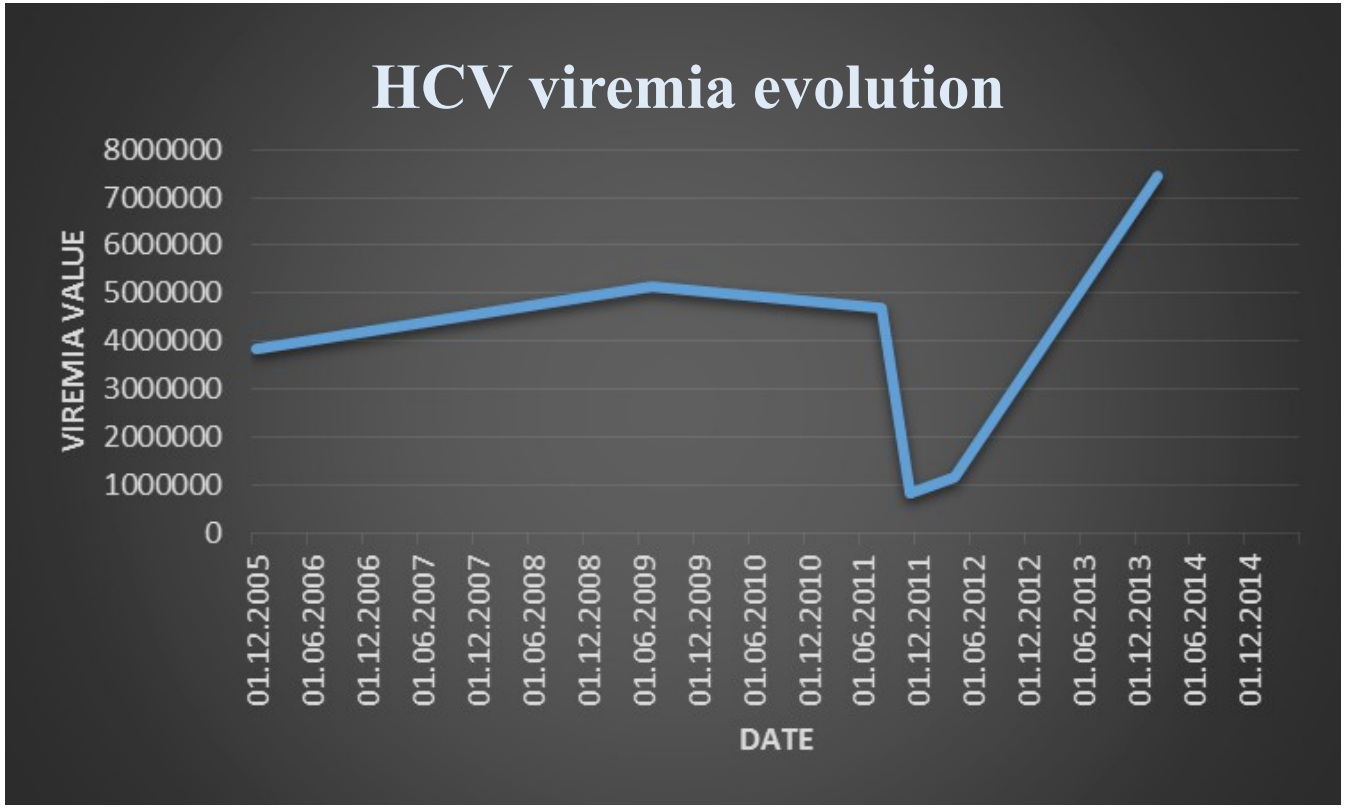
Case report (III) - TREATMENT

Pegasys 180µg/week + RIBAVIRIN 1200mg/day



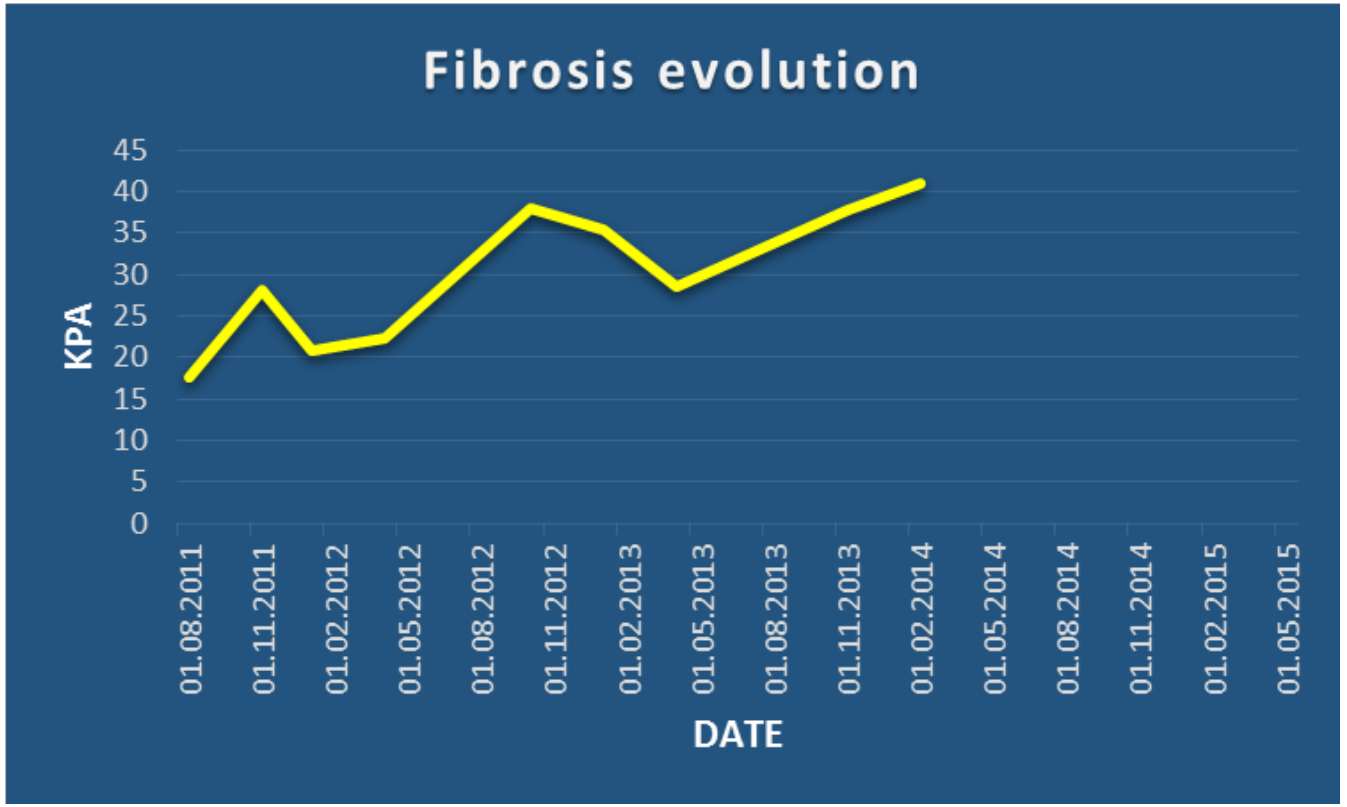
Case report (IV)

Viremia evolution



Case report (V)

Assessment of fibrosis - FibroScan



Case report (VI)

Superior endoscopy

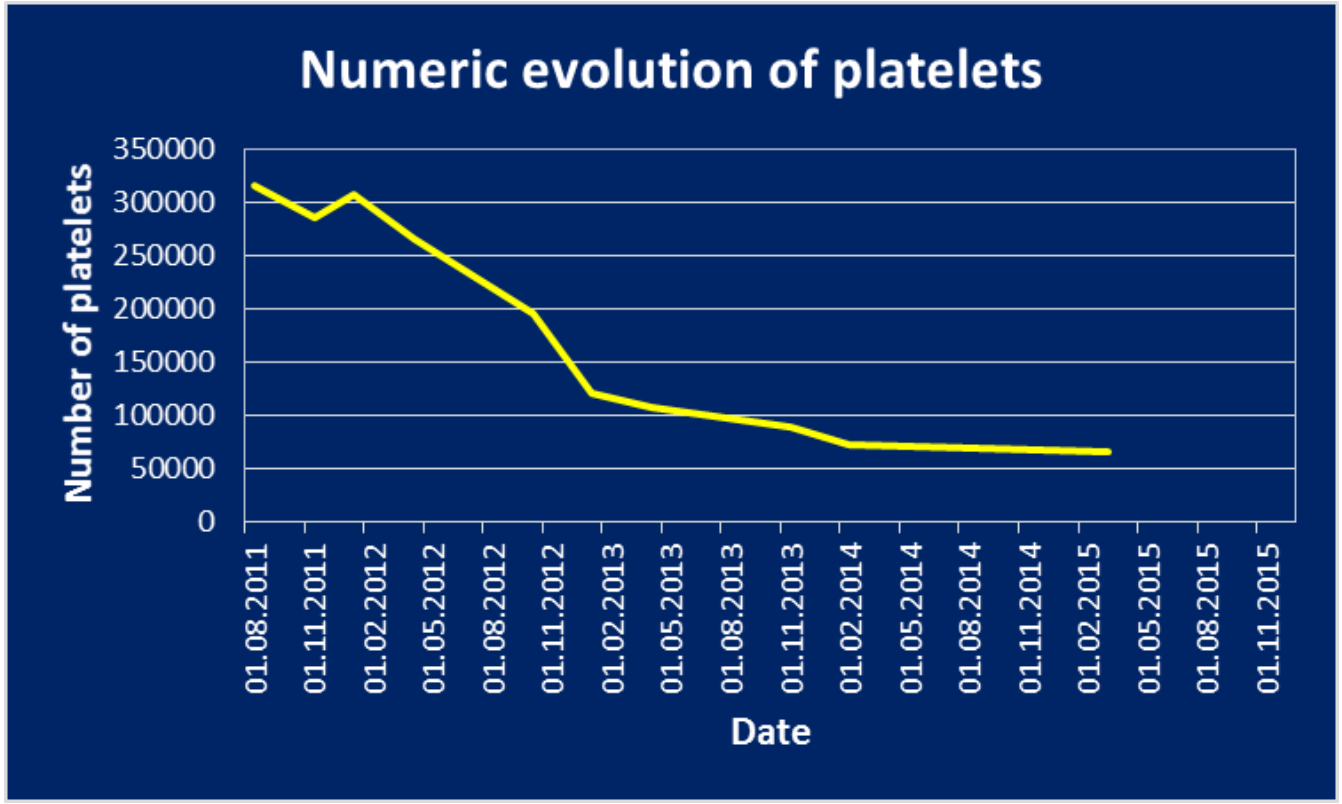
- August 2011 – esophageal varices grade I
- October 2012 – esophageal varices grade II

Case report (VII)

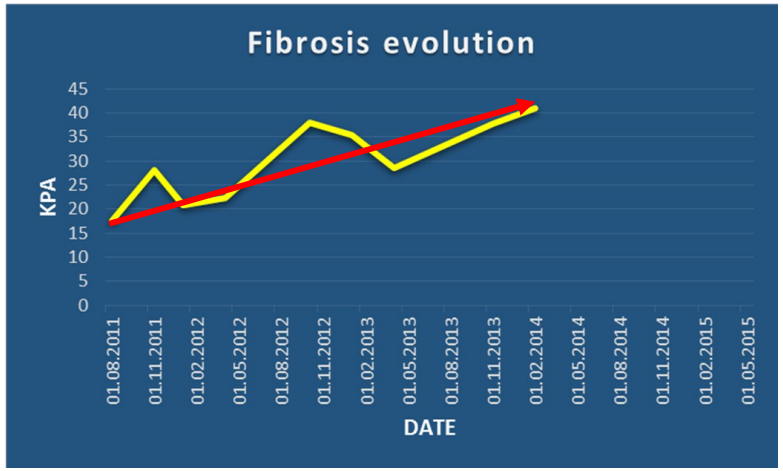
Biological tests

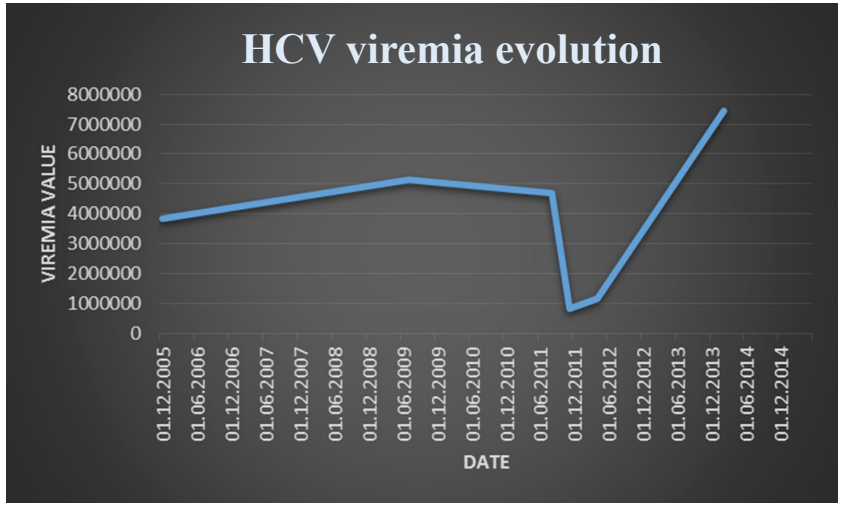
-Hemogram – without anemia and normal leucocytes

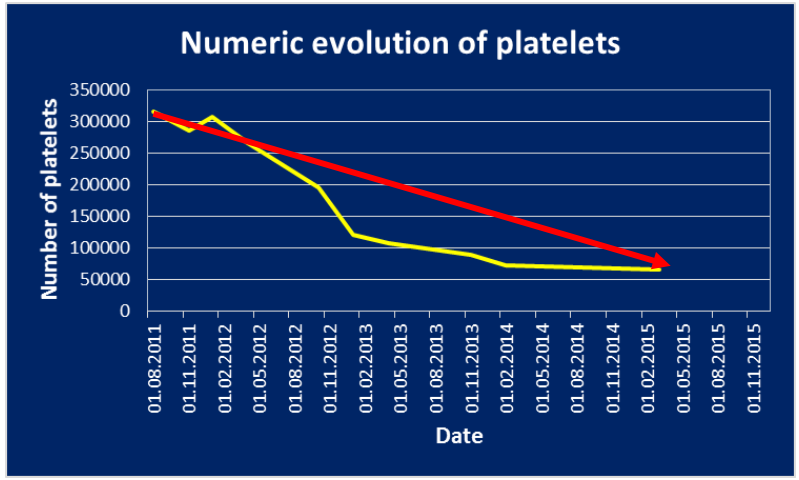
- **Platelets first normal and then in numeric regresion**



Case report (VII)







Case report (VIII)

HCV Liver Cirrhosis, Child-Pugh B (8 points)
NON – RESPONDER to standard Bi-Therapy.

Q 1 – What are we doing next?

- **Until 2011, the combination of pegylated Interferon alpha and ribavirin for 24 or 48 weeks was the approved treatment for chronic hepatitic C[5].**

- **With this regimen, patients infected with genotype 1 has SVR rates of approximatly 40% in North America and 50% in Western Europe[6].**

(5)European Association for the Study of the Liver . EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol 2011; 55: 245-264.
(6)Antaki N, Craxi A, Kamal S, Moucari R, Van der Merwe S, Haffar S et al. The neglected hepatitis C viruf genotype 4, 5 and 6: an international consensus report. Liver Int 2010; 30: 342-355.

- **People with a Child-Pugh B score have significantly impaired liver function and are at high risk for progression to decompensated cirrhosis. They also have a poor prognosis: on average, only 60% of people with Child-Pugh B cirrhosis survive for more than two years once they reach this stage of liver damage.**

- **Effective treatment for people at this stage of liver disease is especially urgent[7].**

(7)Jacobson I et al.Efficacy and safety of grazoprevir and elbasvir in hepatitis C genotype 1-infected patients with Child–Pugh Class b cirrhosis (C-SALT part A). J Hepatology 62 (50th International Liver Congress), S193, abstract O008, 2015.

- In patients with advanced fibrosis and cirrhosis, HCV eradication reduce the rate of decompensation and will reduce, albeit not abolish, the risk of HCC. In these patients, surveillance for HCC should be continued. (A1)

- In patients with decompensated cirrhosis, HCV eradication reduce the need for liver transplantation. (B2)

- Whether HCV eradication impacts mid to long-term survival in these patients is unknown[3]. (B2)

(3)EASL Recommandations on Treatment of Hepatitis C 2015. J Hepatol (2015), http://dx.doi.org/10.1016/j.jhep.2015.03.025..

- **Patients with compensated cirrhosis with contraindications to the use of ribavirin or with poor tolerance to ribavirin, should receive the fixed – dose combination of sofosbuvir (400mg) and ledipasvir (90mg) for 24 weeks without ribavirin.**

- **Patients infected with subtype 1b with cirrhosis should receive this combination for 12 weeks with daily wight based ribavirin. (B1)**

(3)EASL Recommandations on Treatment of Hepatitis C 2015. J Hepatol (2015), http://dx.doi.org/10.1016/j.jhep.2015.03.025..

- **Patients infected with HCV genotype 1 can be treated with an IFN-free regimen comprising the fixed – dose combination of ombitasvir (12.5mg), paritaprevir (75mg) and ritonavir (50mg) in one single tablet and dasabuvir (250mg) (A1).**

- **Pacients infected with subtype 1b with cirrhosis should receive this combination for 12 weeks (A1).**

(3)EASL Recommandations on Treatment of Hepatitis C 2015. J Hepatol (2015), http://dx.doi.org/10.1016/j.jhep.2015.03.025..

- **Patients infected with genotype 1 can be treated with an IFN-free combination of daily sofosbuvir (400mg) and daily simeprevir (150mg) for 12 weeks. (A1)[8]**

- **In patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks (B1).**

(3)EASL Recommandations on Treatment of Hepatitis C 2015. J Hepatol (2015), http://dx.doi.org/10.1016/j.jhep.2015.03.025.

(8)Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A et al. Simeprevir plus sofosbuvir with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment naive patients: the COSMOS randomised study. Lancet 2014; 384: 1756-1765.

- **Patients infected with genotype 1 can be treated with an IFN-free combination of daily sofosbuvir (400mg) and daily daclatasvir (60mg) for 12 weeks. (A1)**

- **In patients with cirrhosis with contra-indications to the use of ribavirin, extending duration of treatment to 24 weeks (B1).**

(3)EASL Recommandations on Treatment of Hepatitis C 2015. J Hepatol (2015), http://dx.doi.org/10.1016/j.jhep.2015.03.025..

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For patients who are NON-RESPONDERs to standard bi-therapy and *for the moment* no other antiviral treatment, we have a waiting list, like the one for liver transplant.

The patients has supportive treatment with ursodeoxicholic acid in chronic hepatits and prevention of portal hypertension, hepatic encefalopathy for liver cirrhosis.

CAN HEPATITIS C TREATMENT BE SAFELY DELAYED?

- Retrospective patient data from the Veterans Administration [VA] were used to estimate the impact on patient risk of treatment initiation before and after the patient's FIB4 levels became elevated.

- Delaying treatment until after a patient's FIB4 level exceeds 3.25 has a clear detrimental effect on treatment effectiveness[9].

(9)J.S. McCombs1, I. Tonnu-MiHara2, T. Matsuda1, J. McGinnis1, S. Fox3. 1Schaeffer Center for Health Policy and Economics, Los Angeles, 2Veterans Administration Healthcare System, Long Beach, 3Keck School of Medicine, University of Southern California, Los Angeles, United States

Q 2 – How often do we need to perform FibroScan or serum markers like FibroMax?

The prediction of intermediate stage of fibrosis in chronic hepatitis C represents a prognostic factor for disease progresion.

There are no studies, there are only international agreements based on personal experience:

- **FibroScan – every 6 months**
- **FibroMax – every 12 months**

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	0 months	3 months	6 months	12 months
HVC Viremia	X	X (if the pacient is treated with the standard bi-therapy)		X (if the pacient is treated with the standard bi-therapy)
HCV Genotype	X			
Il 28b	X			
FibroScan	X		X	X
FibroMax	X			
Ultrasounds	X	X	X	X
AST, ALT	X	X	X	X
Bilirubine	X	X	X	X
Albumine	X	X	X	X
Hemograme	X	X	X	X
Urinary samples	X	X	X	X

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Q 3 – If we have other comorbidities (alcoholism, autoimmunity, dyslipidemia, genetic or metabolic liver diseases, Diabetus Mellitus) do we need to change the intervals of non-invasive assessment of fibrosis?

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Based on our experience, we will not obtain any other information.

Q 4 – Can we detect with FibroScan a liver nodule?

Q 4 – Can we detect with FibroScan a liver nodule?

NO, Transient Elastography can't detect a liver nodule, because it is a focal lesion.

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Conclusions (I)

1. A common characteristic of all chronic liver diseases is the occurrence and progression of fibrosis toward cirrhosis.
2. Liver biopsy remain the gold standard in liver fibrosis evaluation.
3. Non-invasive assesment of liver fibrosis has experienced explosive growth in recent years.
4. The FibroTest (FibroSure in USA) is the most widely validated indirect serum marker panel.

Conclusions (II)

5. The FibroScan is the most widely used non-invasive method in Europe.

6. For patients with chronic HCV infection, non-responder to standard therapy with peg-IFN plus RIBA, we have a lot of possibilities of treatment, using EASL 2015 Recommandations.

7. If we do not have available the new IFN-free therapies, we should have a waiting list with non-responders or relapser HCV patients and supportive treatments.

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Lessons to take home !

1. Assessment of liver fibrosis is a crucial moment for our pacients.
2. Liver fibrosis is an evolutive, progressiv process, but also a regressive process.
3. Utilization of non-invasive biomarkers for liver histology can significantly reduce, but not completly replace the requirment for liver biopsies in patients with chronic viral hepatitis.
4. Our case prove that liver fibrosis progress in absence of anti HCV treatment as fibrosis measurement by FibroScan have shown.