Karaciğer Transplantlı Hastada HCV Yönetimi

Dr. Zeki Karasu
Ege Üniversitesi Tıp Fakültesi

Karaciğer Nakli Sebepleri Arasında HCV Sıklığı

Batılı ülkelerde	Ülkemizde
%25-50	%10-20

Karaciğer Nakli Sebepleri Arasında HCV Sıklığı

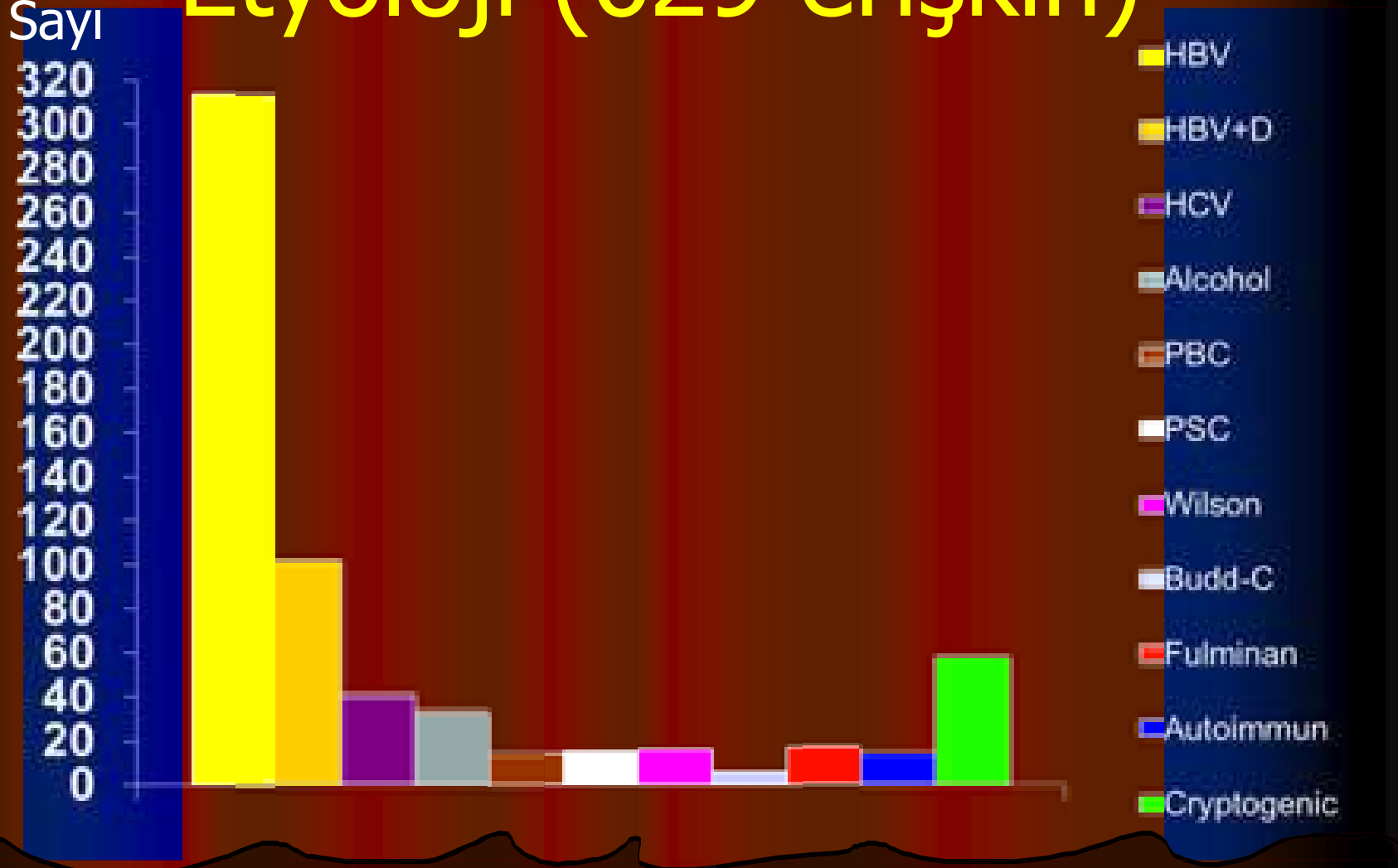
ABD

1991: % 16.4

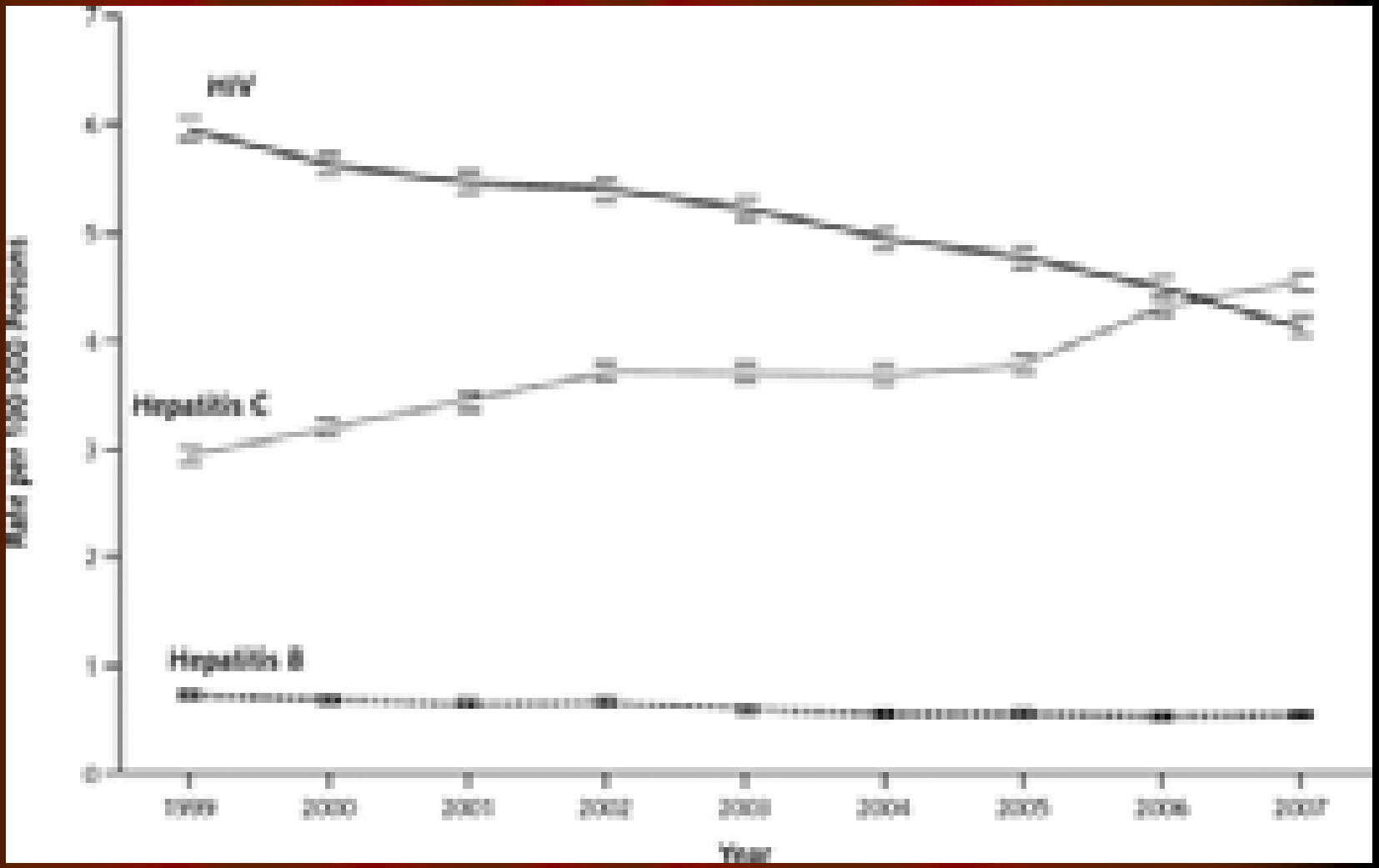
2001: % 54.7

Thuluvath P. Trends in Post-Liver Transplant Survival in Patients With Hepatitis C Between 1991 and 2001 in the United States. Liver Transplantation 2007

Ege Üniversitesi Deneyimi Etyoloji (629 erişkin)



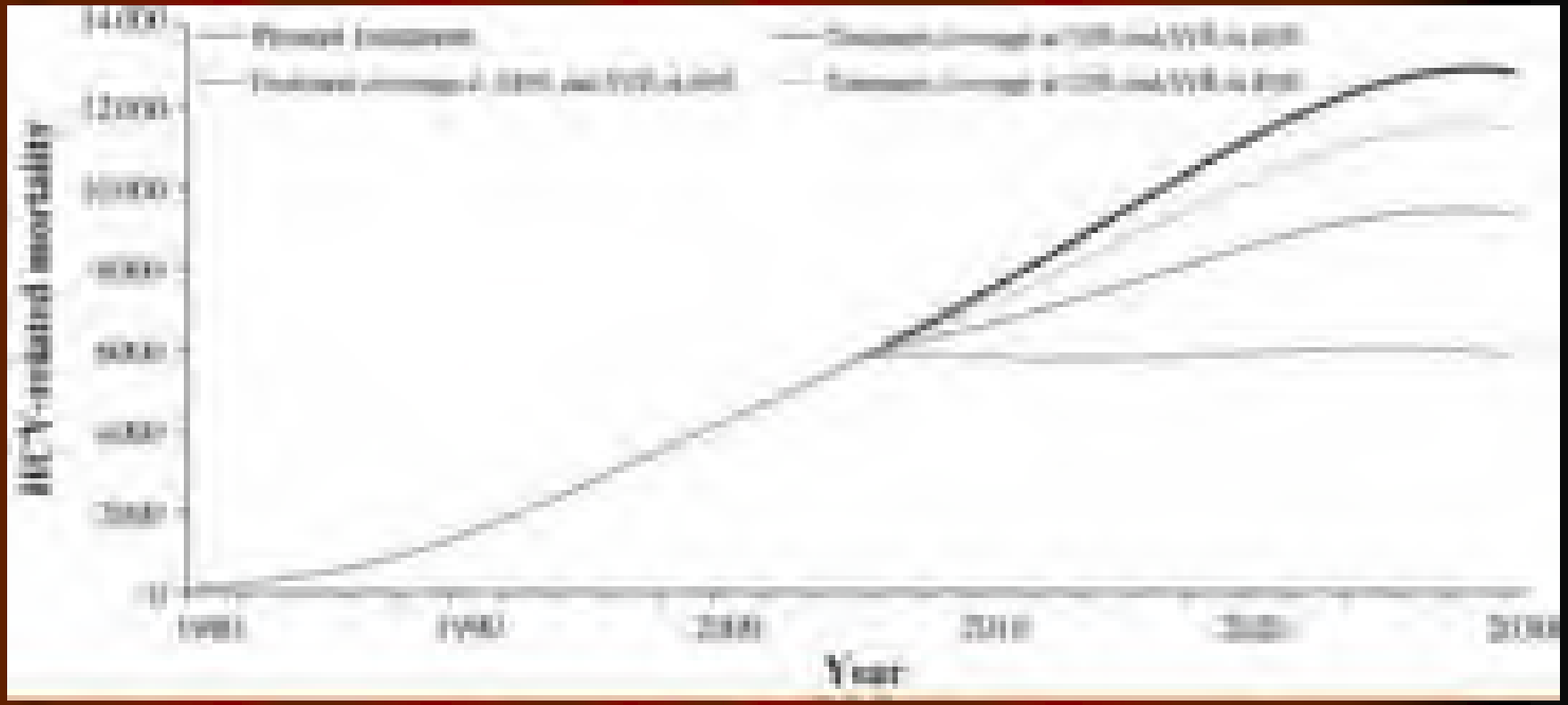
Annual age-adjusted mortality rates from hepatitis B and hepatitis C virus and HIV infections listed as causes of death in the United States between 1999 and 2007.Because a decedent can have multiple causes of death, a record listing more than 1 type of inf...



Ly K N et al. Ann Intern Med 2012;156:271-278

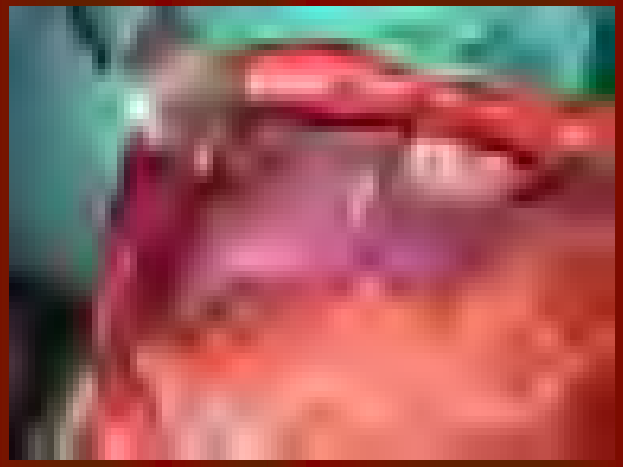
Annals of Internal Medicine

HCV nedenli mortalite tahminleri

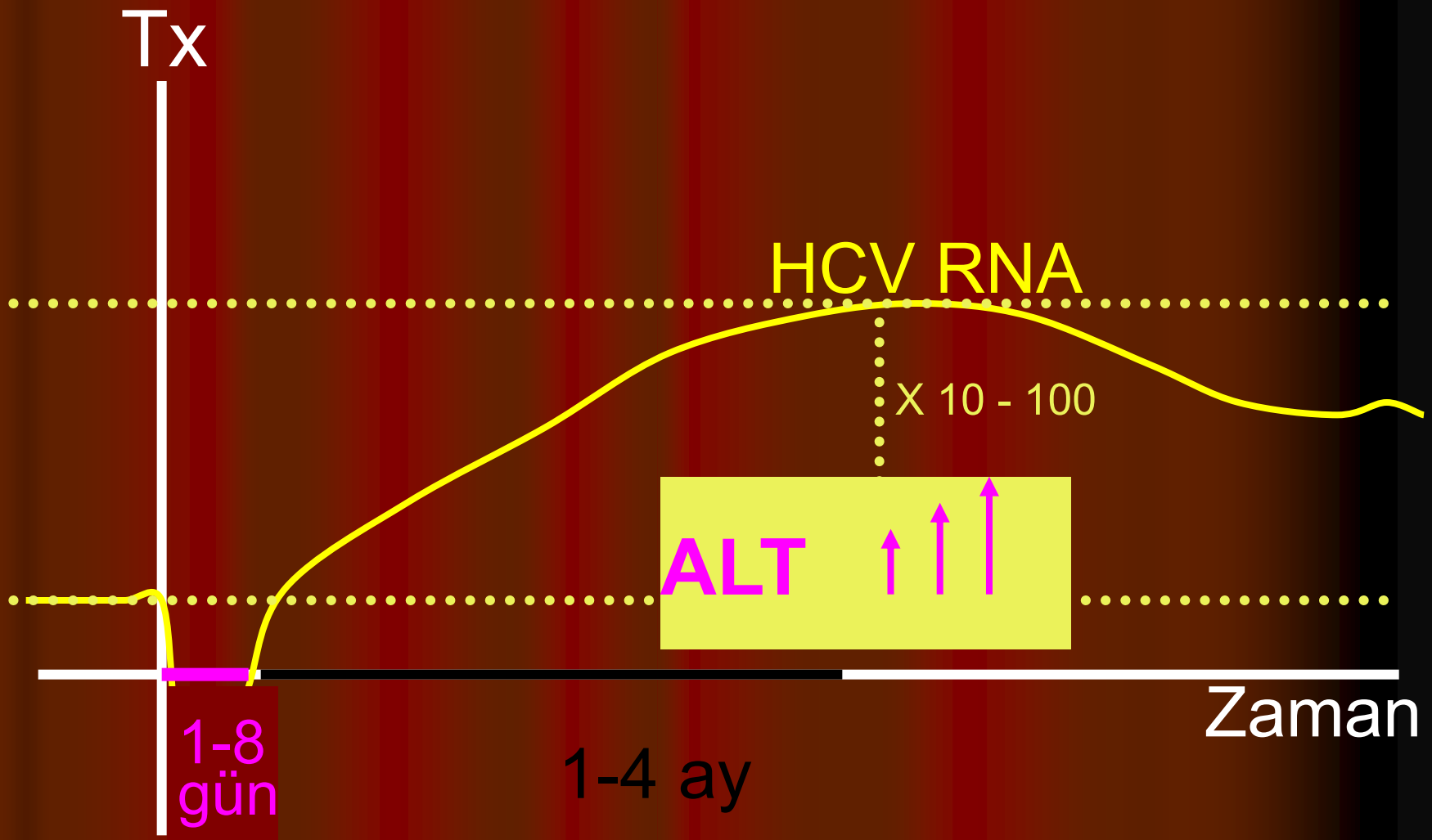


Deuffic-Burban S, et al. Estimating the future health burden of chronic hepatitis C and human immunodeficiency virus infections in the United States. J Viral Hepat. 2007

HCV-RNA
(+)



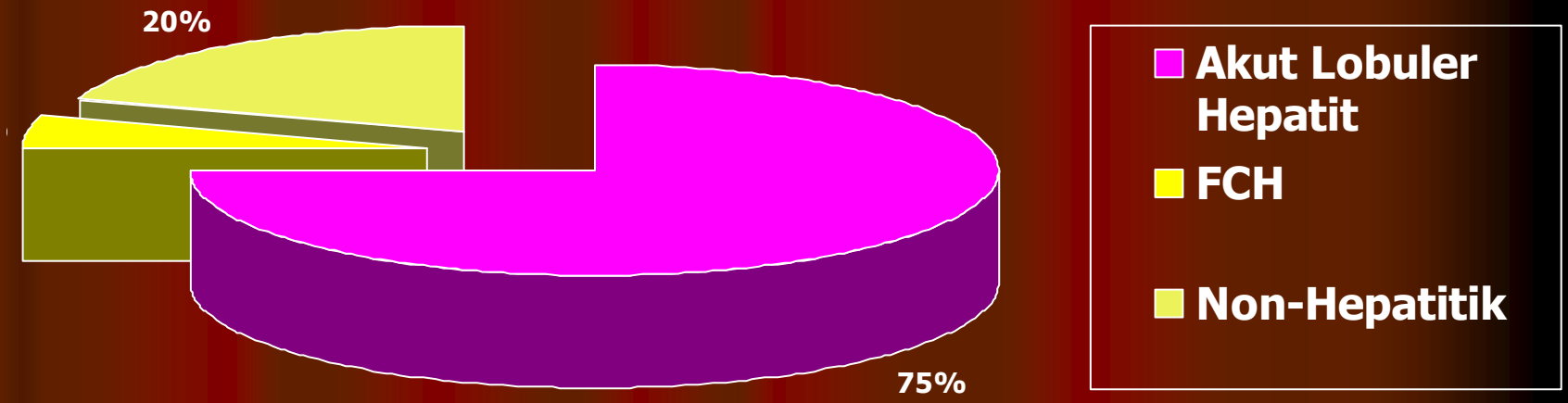
HCV-RNA
(+)



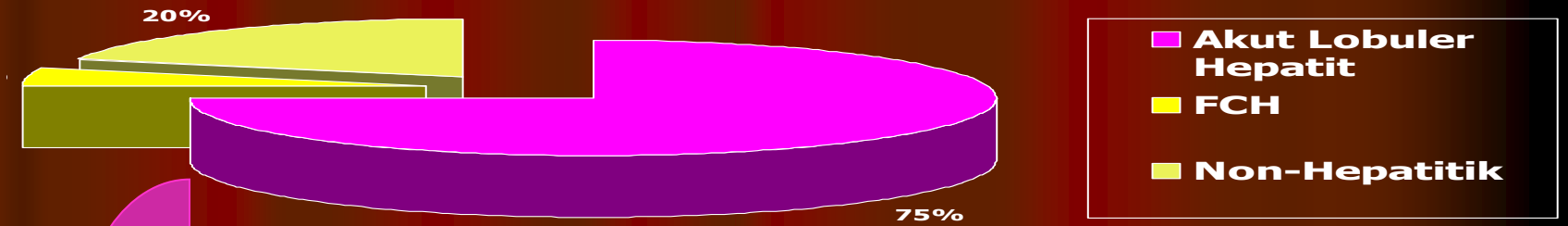
Chazouilleres O. Gastroenterology 1994;106:994-999.
Gane EJ. Gastroenterology 1996;110:167-177.
Di Martino V. Hepatology 1997;26:1344 1350.
Fukumoto T. Hepatology. 1996;24:1351-1354

Northup PG, AASLD 2006

Karaciğer Nakli Sonrası HCV'nin Klinik Seyri



Karaciğer Nakli Sonrası HCV'nin Klinik Seyri

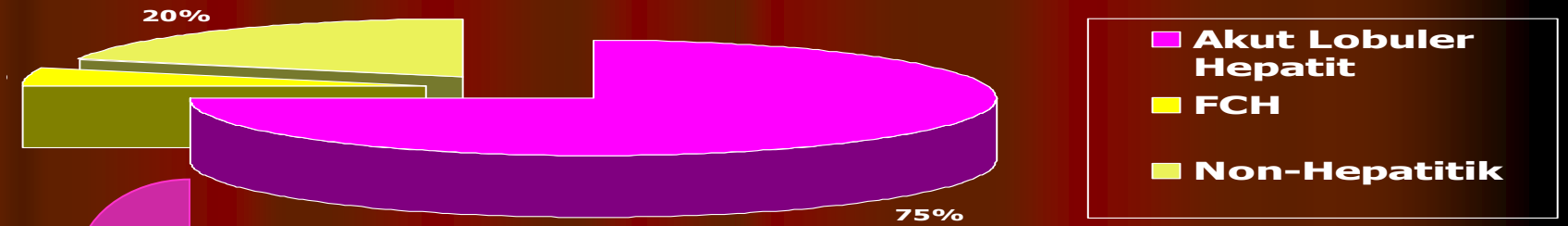


Kronik Hepatit

% 25 3-5 yılda
% 25 daha yavaş

Siroz

Karaciğer Nakli Sonrası HCV'nin Klinik Seyri



Kronik Hepatit

% 25 3-5 yılda
% 25 daha yavaş

Siroz

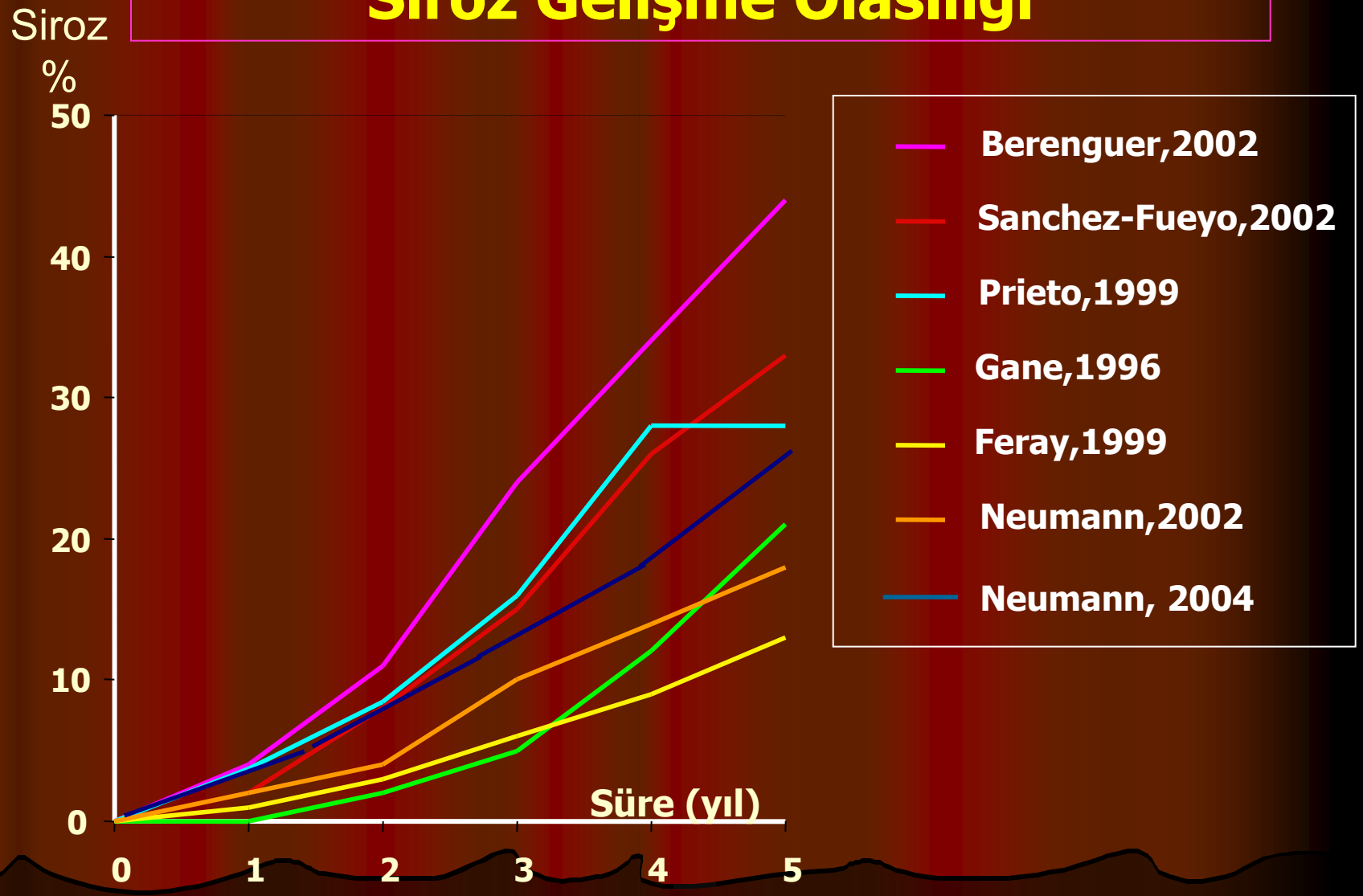
4 yıl

% 75

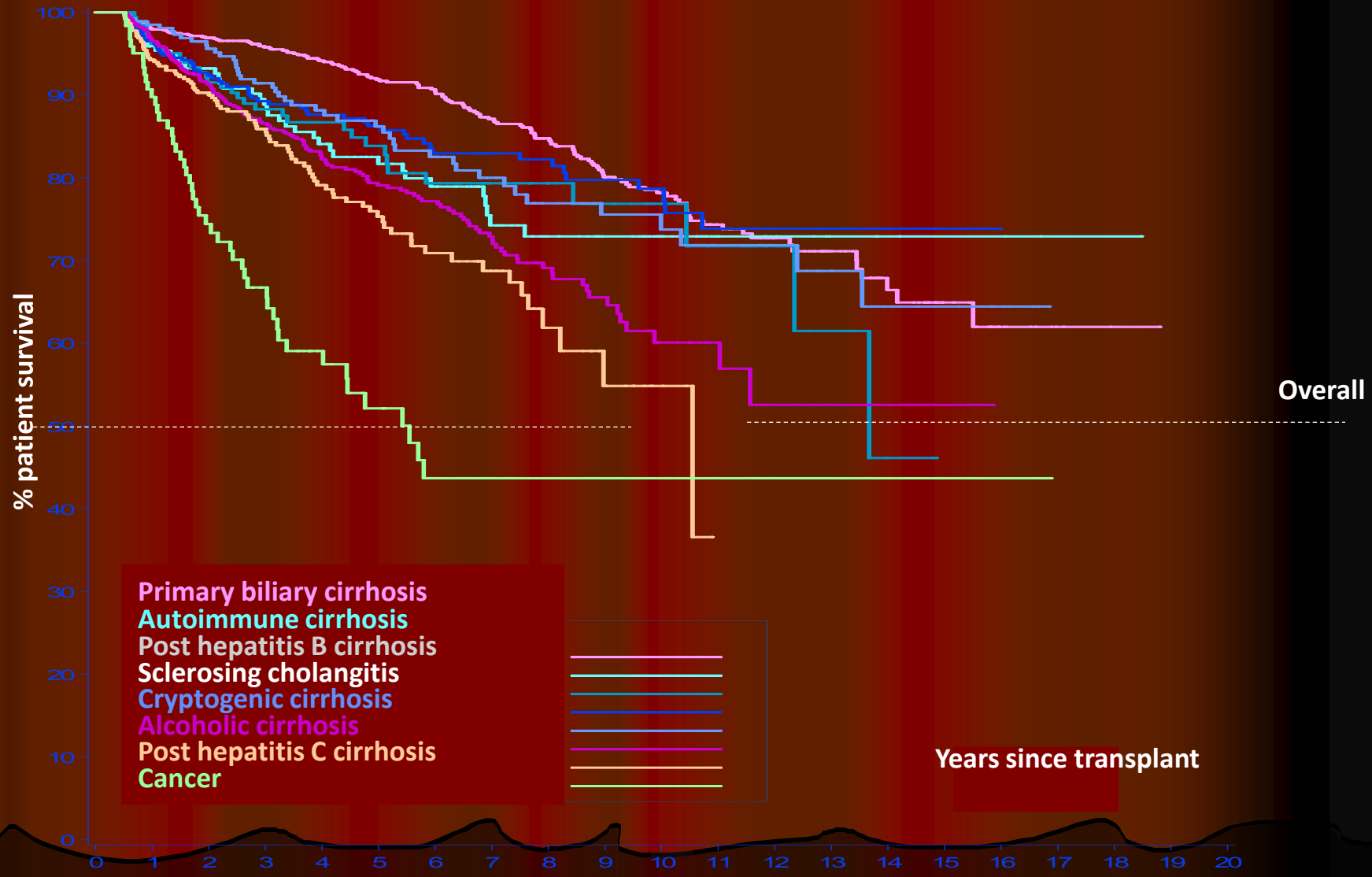
Dekompanzasyon

sağkalım
3 yıl %20

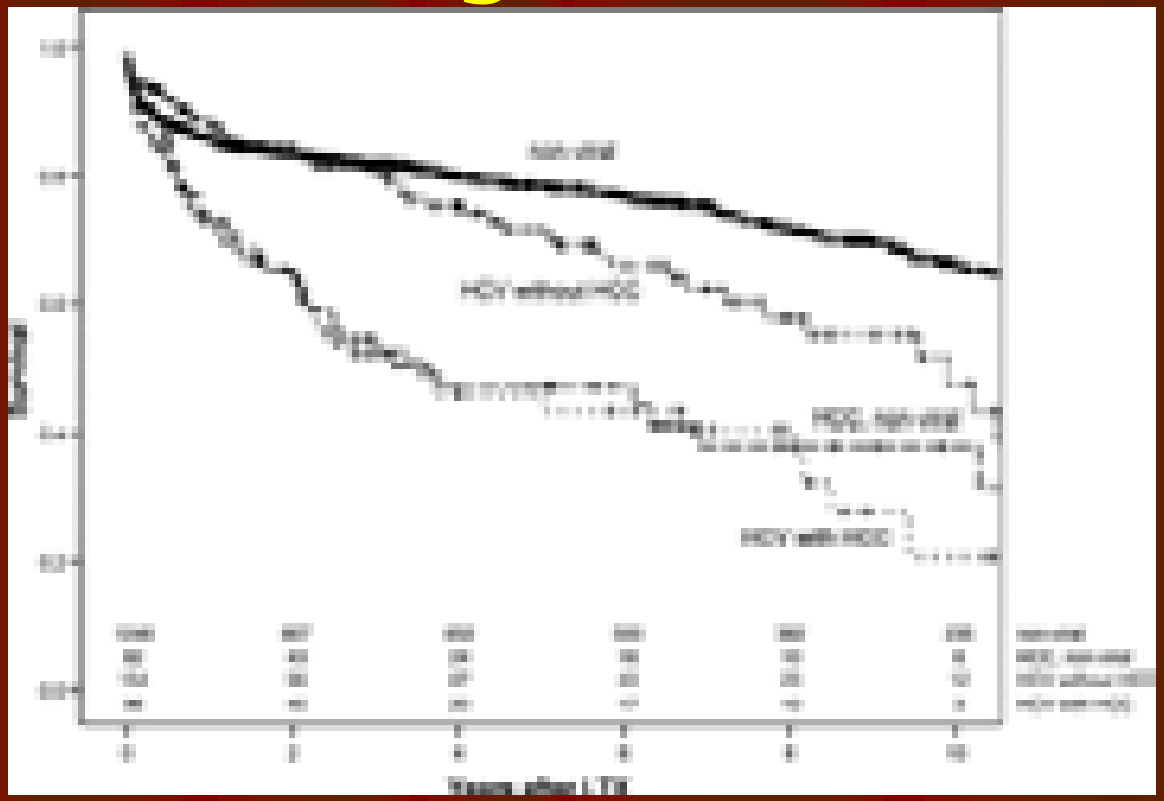
HCV'li Hastalarda Transplant Sonrası Siroz Gelişme Olasılığı



Karaciğer Nakli Sonrası Sağ Kalım

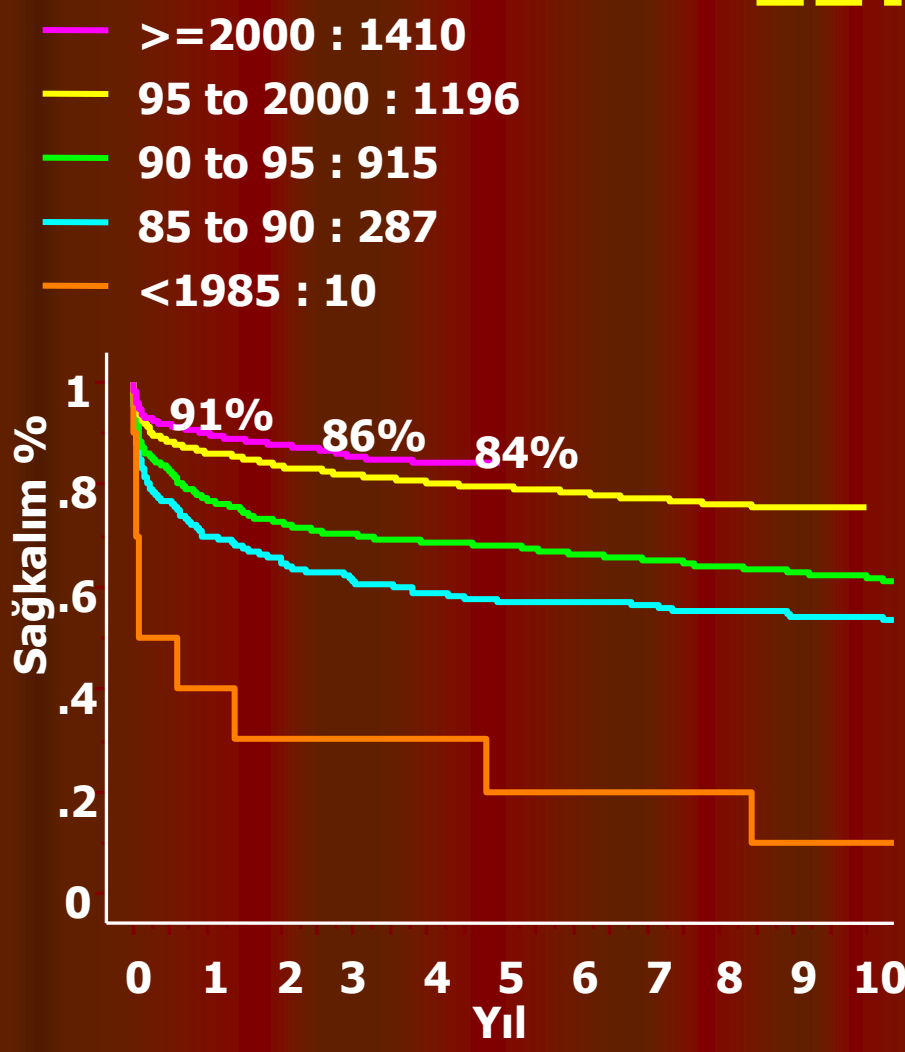


HCV'de Karaciğer Nakli Sonrası Sağ Kalım

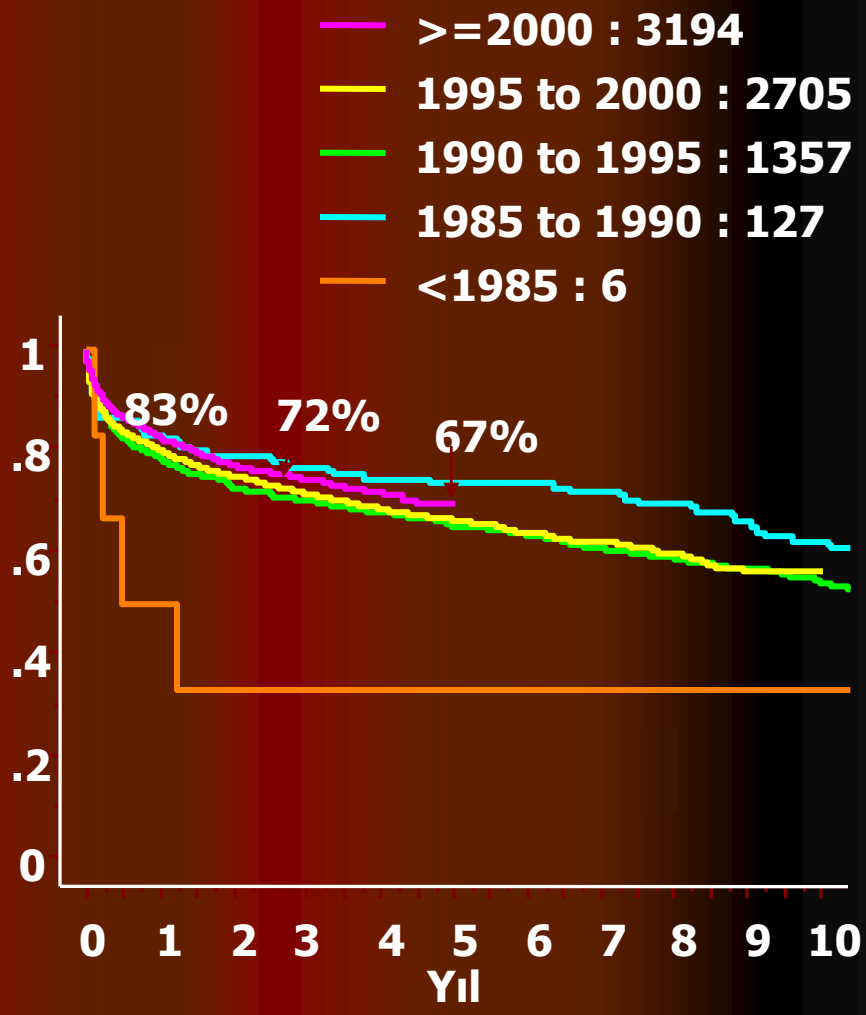


Melum E. et al. Hepatitis C impairs survival following liver transplantation irrespective of concomitant hepatocellular carcinoma. J Hepatol 2007

ELTR

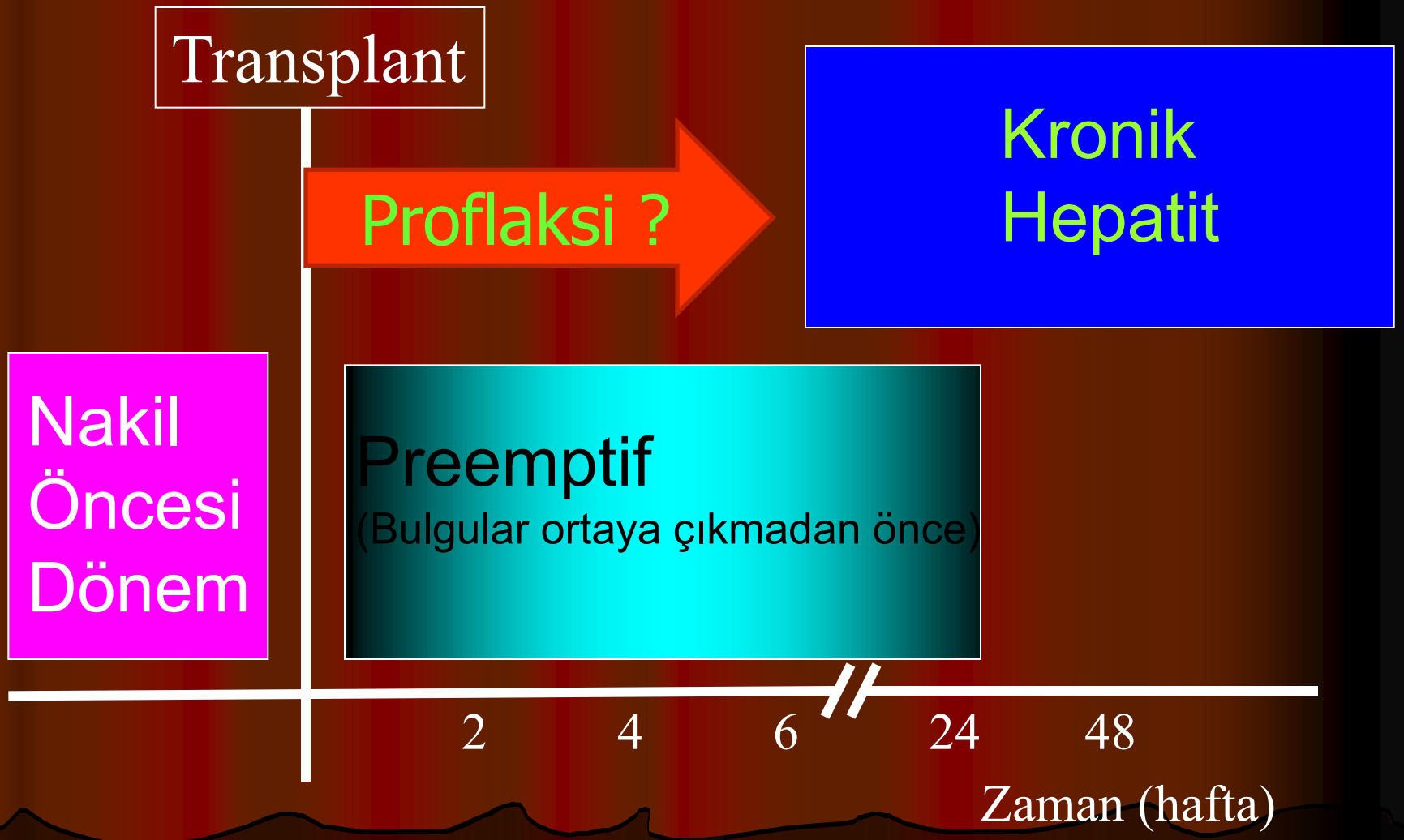

>=2000 : 1410
95 to 2000 : 1196
90 to 95 : 915
85 to 90 : 287
<1985 : 10
Sağkalım %
1
.8
.6
.4
.2
0
91%
86%
84%
0 1 2 3 4 5 6 7 8 9 10
Yıl

HBV


>=2000 : 3194
1995 to 2000 : 2705
1990 to 1995 : 1357
1985 to 1990 : 127
<1985 : 6
1
.8
.6
.4
.2
0
83%
72%
67%
0 1 2 3 4 5 6 7 8 9 10
Yıl

HCV

Anti viral tedaviye ne zaman başlamalı



Proflaktik tedavi

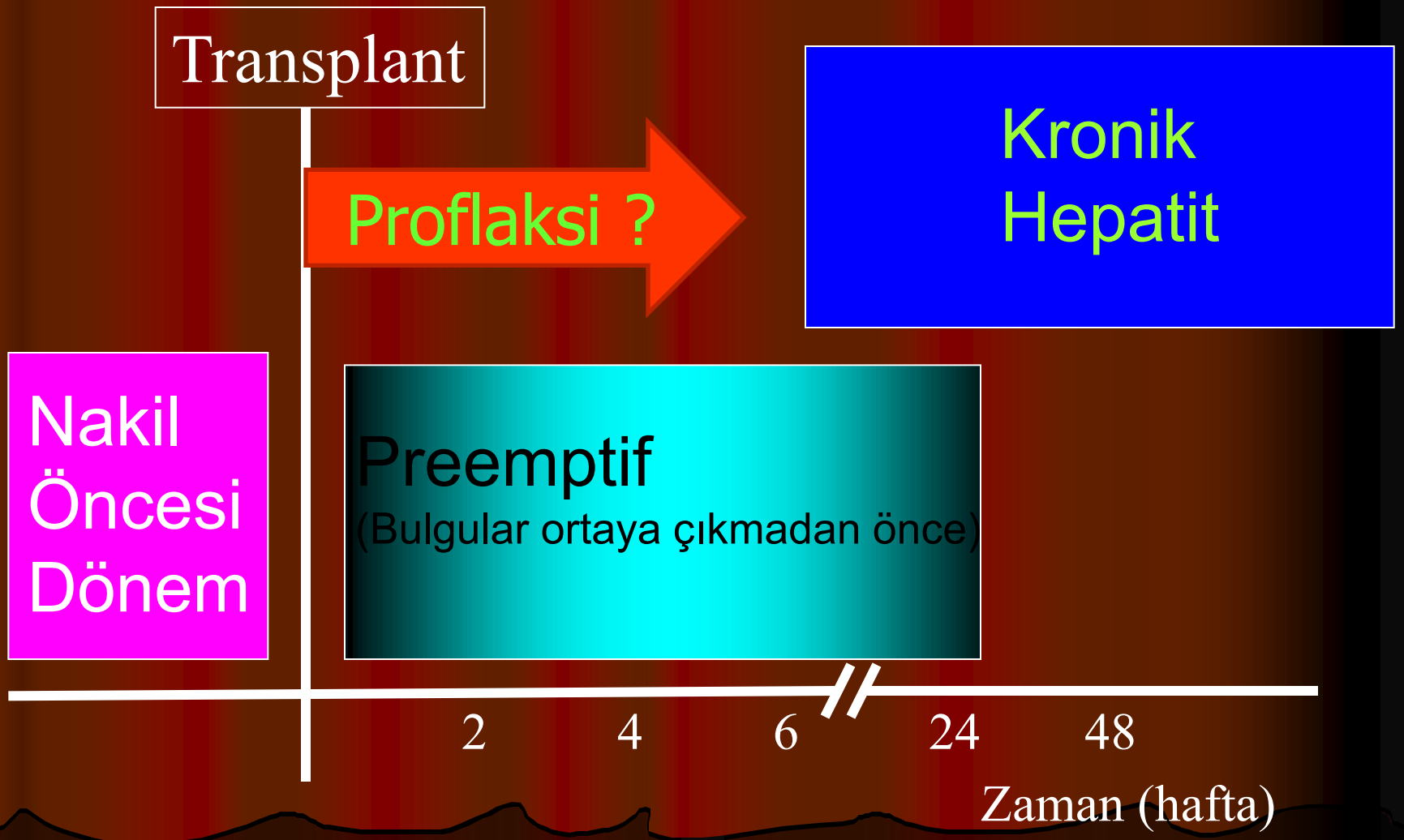
Immünglobulinler

- Şempanzelerde olumlu sonuçlar
- İnsanda anti E2 Ab içeren insan kaynaklı HCIG (Civacir) etkisiz
- Yüksek doz monoklonal E2 antikorları etkisiz
- E1 ve E2 epitoplarına karşı Ab + aşı ?

Schiano et al Liver Transpl 2006

Davis GL Liver Transpl 2006

Anti viral tedaviye ne zaman başlamalı



Hemen KCT sonrası başlanan anti HCV tedaviler

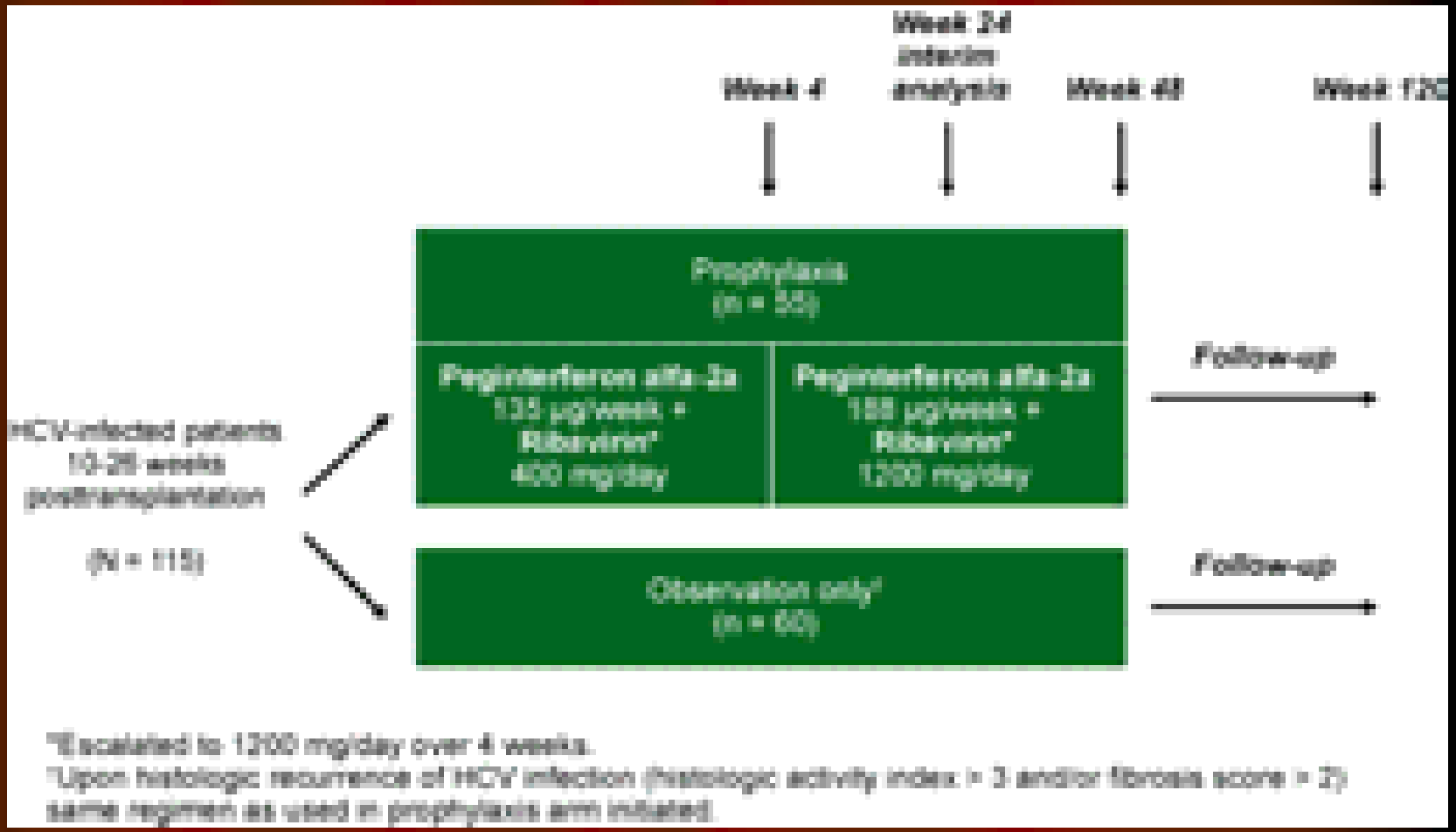
Olumlu faktörler

- Akut HCV: %90 kalıcı virolojik yanıt
- Viremi seviyesi en düşük durumdadır
- İmmunosupresif tedavi henüz yeni başlamıştır

Olumsuz faktörler

- Trombositopeninin en ciddi olduğu dönem
- Bakteriyel infeksiyonların sık görülmesi
- Akut rejeksiyon olasılığının artması ???

PEG-IFN + Ribavirin: Proflaktik Tedavi



Charlton MR, et al. Prophylactic peginterferon alfa-2a/ribavirin vs no prophylaxis following orthotopic liver transplantation (OLT) for hepatitis C: 24-week virologic and safety responses. AASLD 2007

PEG-IFN + Ribavirin: Proflaktik Tedavi

	Virolojik Yanıt (< 50 IU/mL)	
	Proflaksi	Rekürren HCV tedavisi
4. Hafta	7.3	0
12. Hafta	22	33
24. Hafta	38	42

Charlton MR, et al. Prophylactic peginterferon alfa-2a/ribavirin vs no prophylaxis following orthotopic liver transplantation (OLT) for hepatitis C: 24-week virologic and safety responses. AASLD 2007

PEG-IFN + Ribavirin: Proflaktik Tedavi

	Virolojik Yanıt (< 50 IU/mL)	
	Proflaksi	**Rekürren HCV tedavisi**
4. Hafta	7.3	0
12. Hafta	22	33
24. Hafta	38	42
	ALT normalleşmesi	
4. Hafta	44	42
12. Hafta	64	58
24. Hafta	69	67

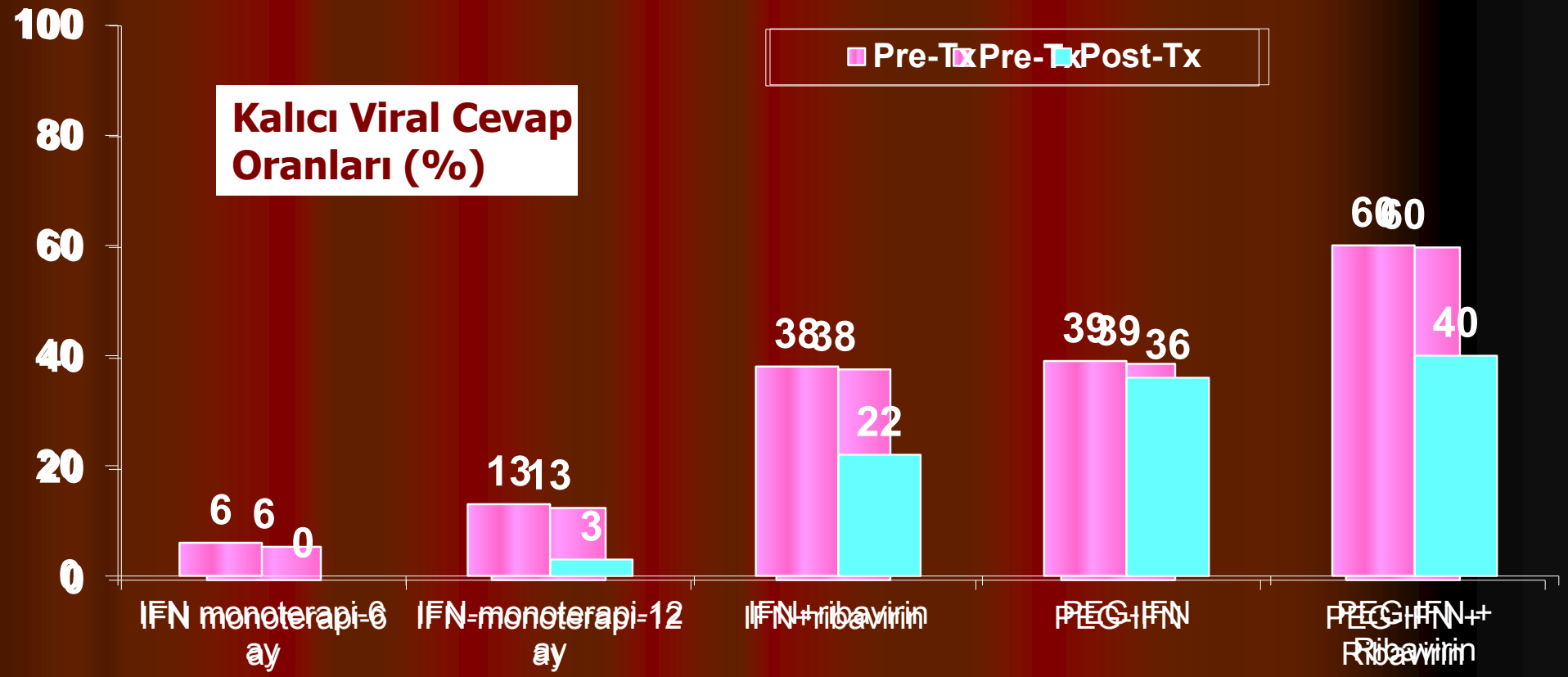
Charlton MR, et al. Prophylactic peginterferon alfa-2a/ribavirin vs no prophylaxis following orthotopic liver transplantation (OLT) for hepatitis C: 24-week virologic and safety responses. AASLD 2007

KCTx sonrası PEGIFN + Ribavirin

Çalışma sayısı	**7**
Hasta sayısı	1184
Genotip 1	%81
SVR ortalama (range)	%36 (%18-50)
5 yıl sağ kalım	SVR (+): % 94 SVR (-): % 69.5

Rendina M. Et al. Facing HCV recurrence after liver transplantation: antiviral therapy response and clinical outcome. Digestive and Liver Disease Supplements **5**(1):30-35 (2011)

Kc nakli sonrası hepatit C tedavisi

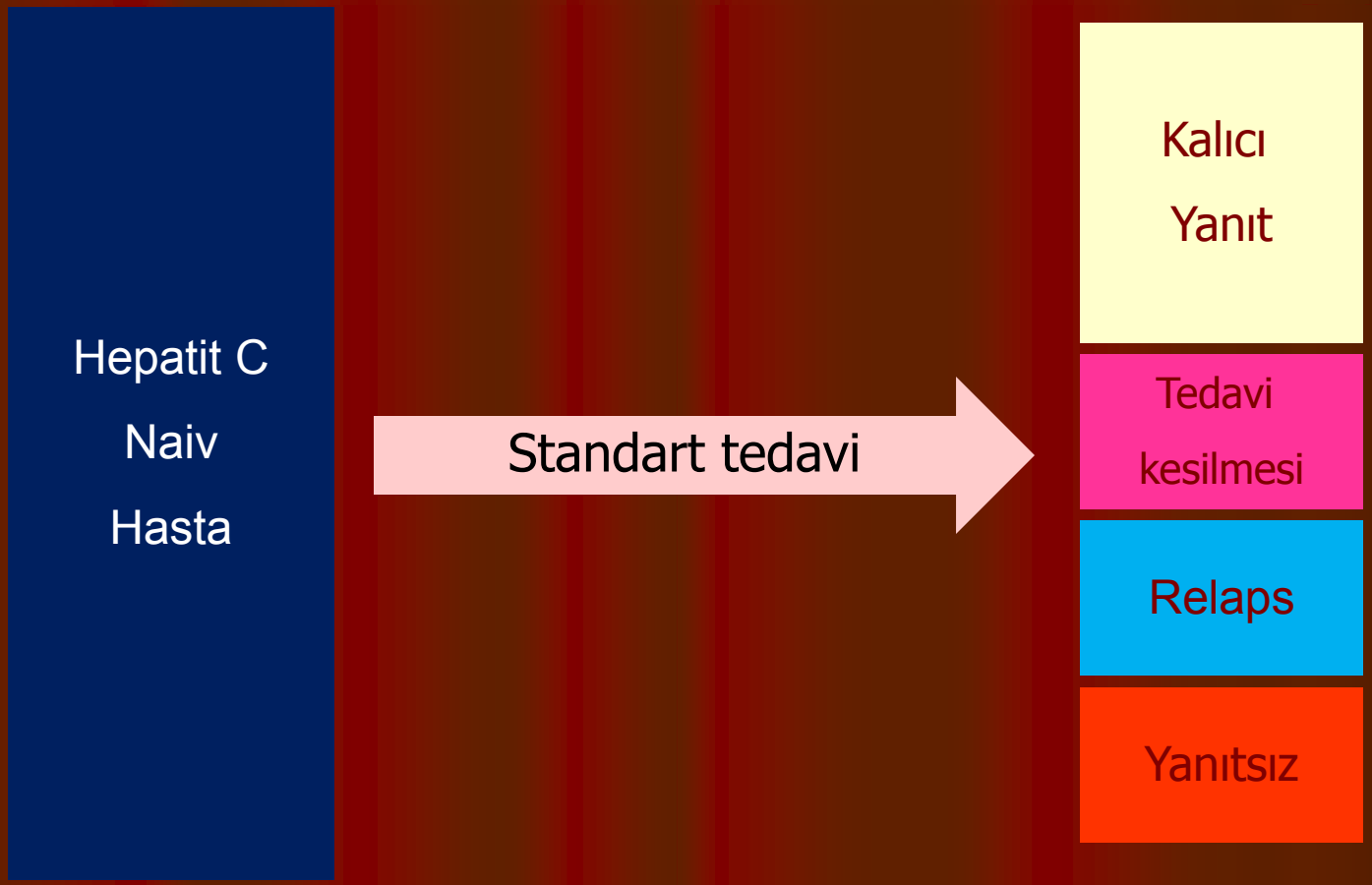


Gane E. Liver Transpl 2002
Terrault and Berenguer Liver Transplant 2006

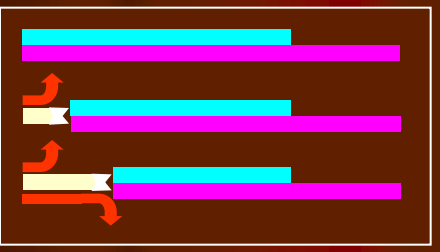
KCTx sonrası PEGIFN + Ribavirin

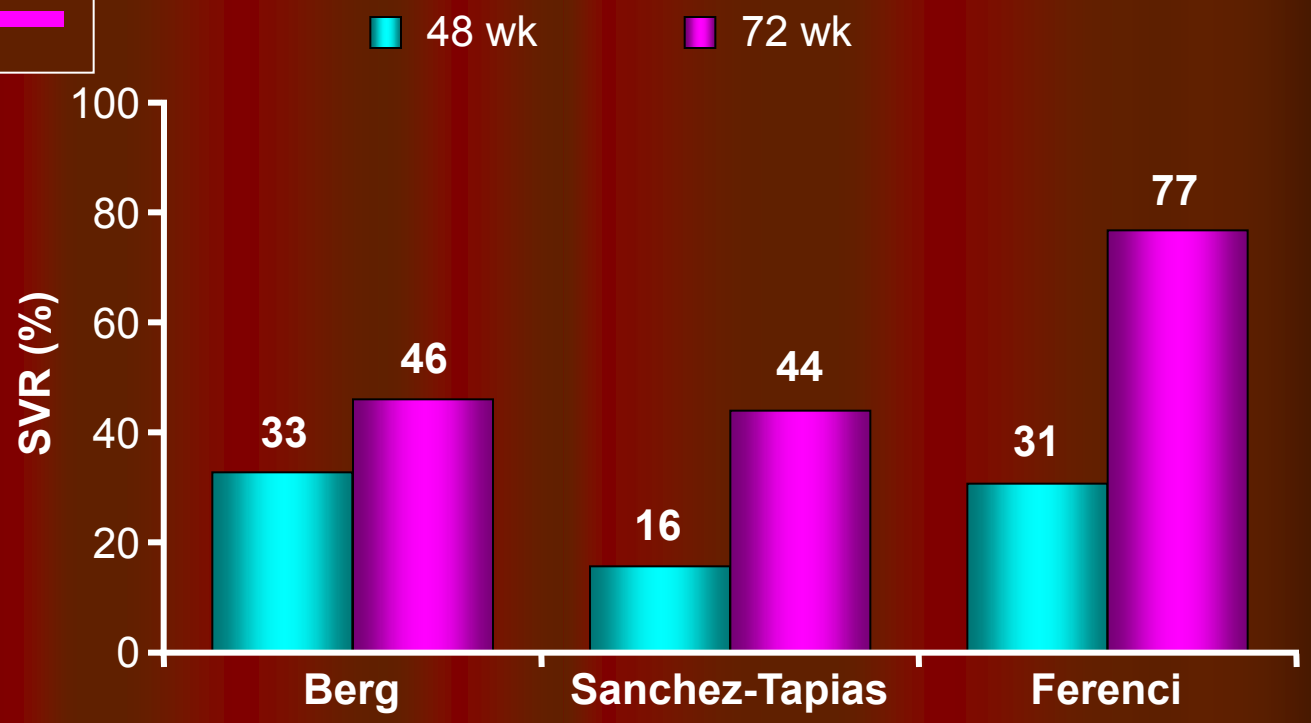
		Hasta sayısı	EOT (%)	SVR (%)
Rodriguez-Luna	Transplantation 2004	19	37	26
Neff (N/NR)	Transplantation 2004	57	28	21
Ross	Clin Transplant 2004	16	38	19
Dumortier	J. Hepatology 2004	20	55	45
Mukherjee	Transplant[illegible]ced 20[illegible]		41	
Castells	J. Hepatology 2005	24	58	33
Neumann	Transplantation 2006	24	68	36
Mukherjee	Hepatogas[illegible]terolog[illegible]2006		41	
Mukherjee	Liver International 2006	39	50	33
Berenguer (a/b)	Liver Transplant 2006	67	46	33
Biselli	Dig liver Dis 2006	11	45	45
Fernandez	Liver Transplant 2006	47	46	23
Chadalavada	Transplantation 2006	92	22	12
Chadalavada	Transplantation 2006	68	24	19
Oton	Am J Transplant. 2006	55	67	44
Carrión	Gastroenterology 2007	81		33
Bizollon (R/NR)	Am J Transplant. 2007	27	37	30
Zimmermann	Transplant International 2007	26	35	19

Hepatit C: Tedaviye Yanıt



Geç Yanıtlılarda Uzatılmış Tedavi





Berg T, et al. Gastroenterology. 2006.
Sanchez-Tapias JM, et al. Gastroenterology. 2006
Ferenci P, et al.

Ege Üniversitesi Deneyimi

13 Hasta

IFN / PEG IFN + Ribavirin

2 Dropout
1 RNA (-)

5 HCV RNA (+)

6 HCV RNA (-)

↓

3 yıl tedavi

↓

HCV RNA (-)

Karasu Z ve ark. APASL 2007

21 Hasta

PEG-IFN + Ribavirin

3 HCV RNA (+)

4 HCV RNA (+)

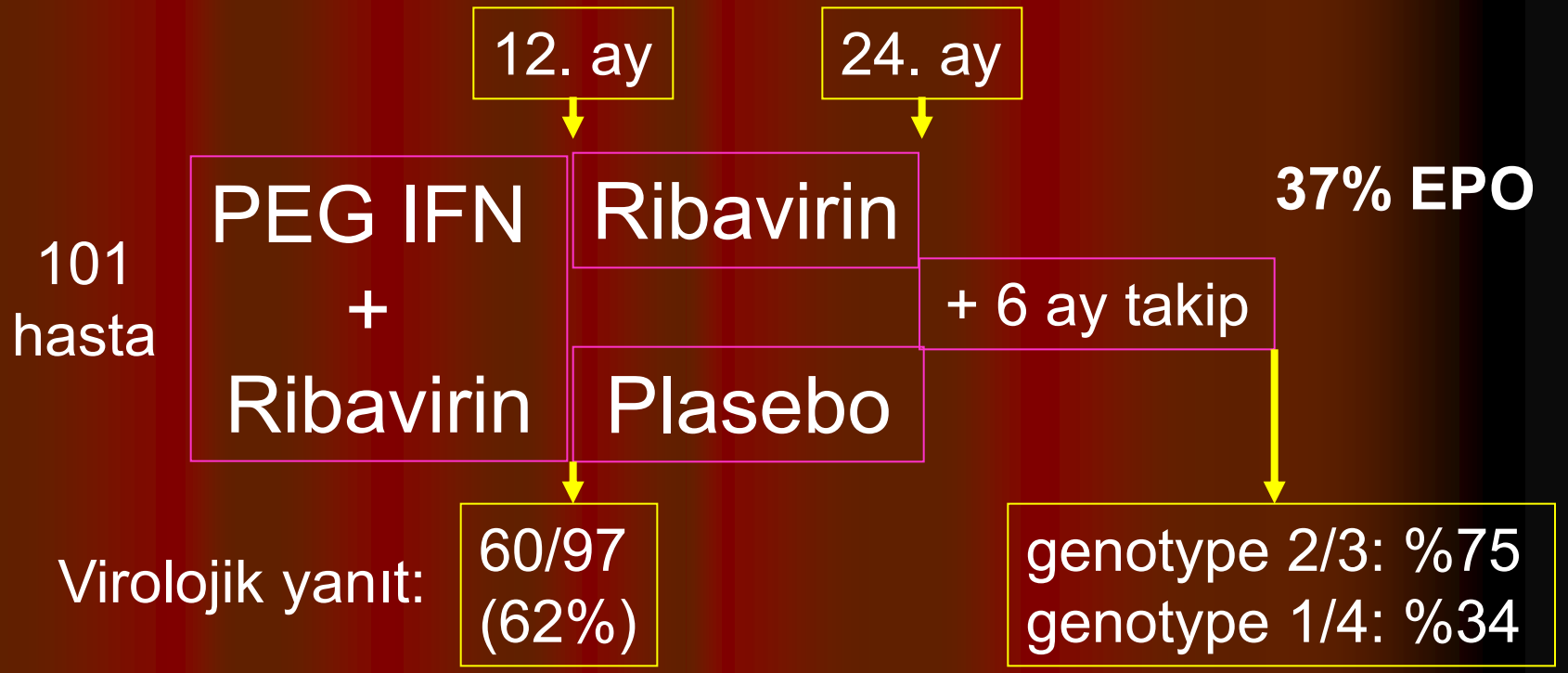
14 HCV RNA (-)

49 (24-77) ay tedavi

66 (20-94) ay tedavi

13 HCV RNA (-)

Kornberg A. Journal of Gastroenterology and Hepatology 2007



creatinine (µmol/L) < 130: %64
> 130: %33

Calmus Y, et al. Peginterferon/Ribavirin With or Without Ribavirin Maintenance Yields High Rates of Virologic Suppression in Individuals With HCV Recurrence Following OLT. AASLD 2006

Survival Without Cirrhosis In HCV+ve Liver Transplant PatientsWith or Without SVR

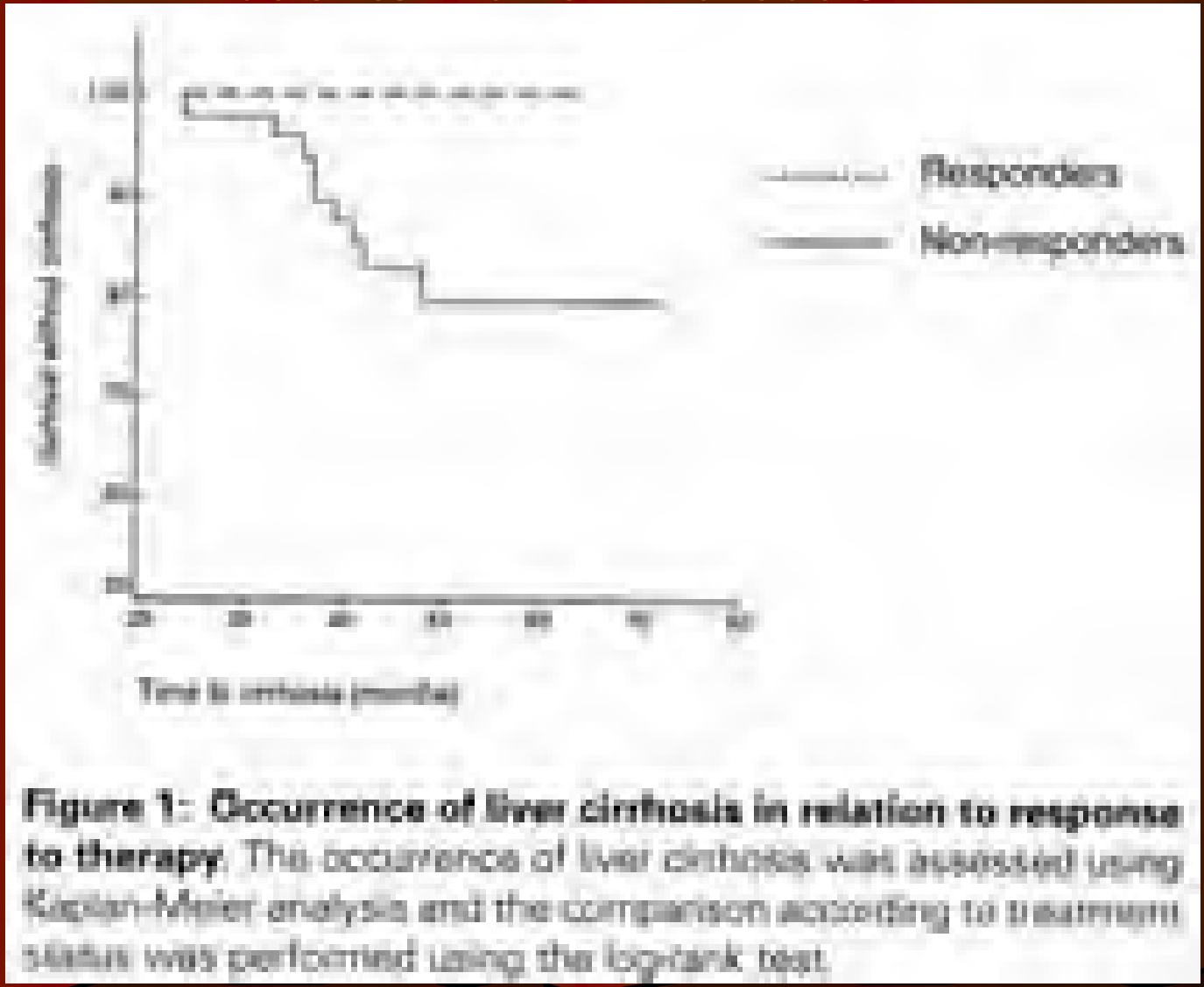


Figure 1: Occurrence of liver cirrhosis in relation to response to therapy. The occurrence of liver cirrhosis was assessed using Kaplan-Meier analysis and the comparison according to treatment status was performed using the log-rank test.

Bizollon AJT 2005; 6: 449-458

1 ve 5 yıl graft ve hasta sağkalımı arasında fark yok

"HCV nüksü ve hastalığın seyri açısından LDLT ile DDLT arasında fark yoktur"

Rakela J J Hepatol 2006, Suguwara Y, Makuuchi M. WJG 2006, Guo Liver Transpl 2006, Biggins SW, Terrault NA Infect Dis Clin N Am 2006 , Berenguer Liver Transpl 2006

Hızlı klinik seyirden sorumlu olabilecek faktörler

Organ donör ve alıcısının yaşı

Organ donör ve alıcısında IL28B

Cinsiyet

KCT öncesi HCV konsantrasyonu

HCV genotipi

HCV quasispecies

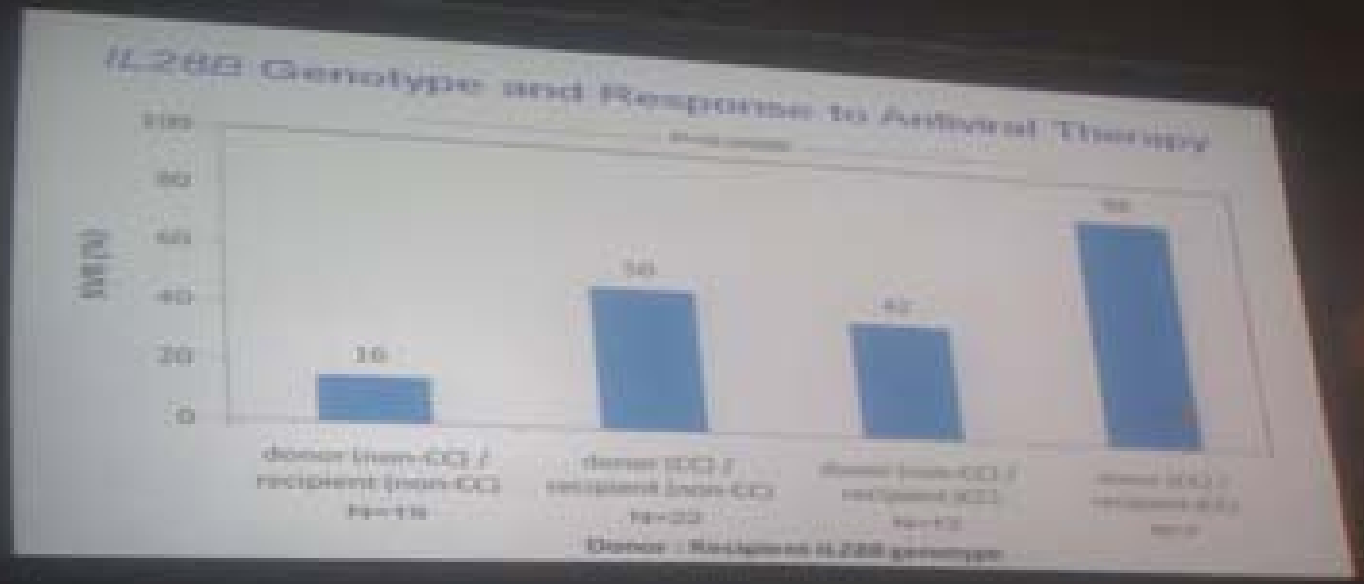
Donör ve alıcının histocompatibilitesi

Eşzamanlı başka bir KC hastalığının varlığı

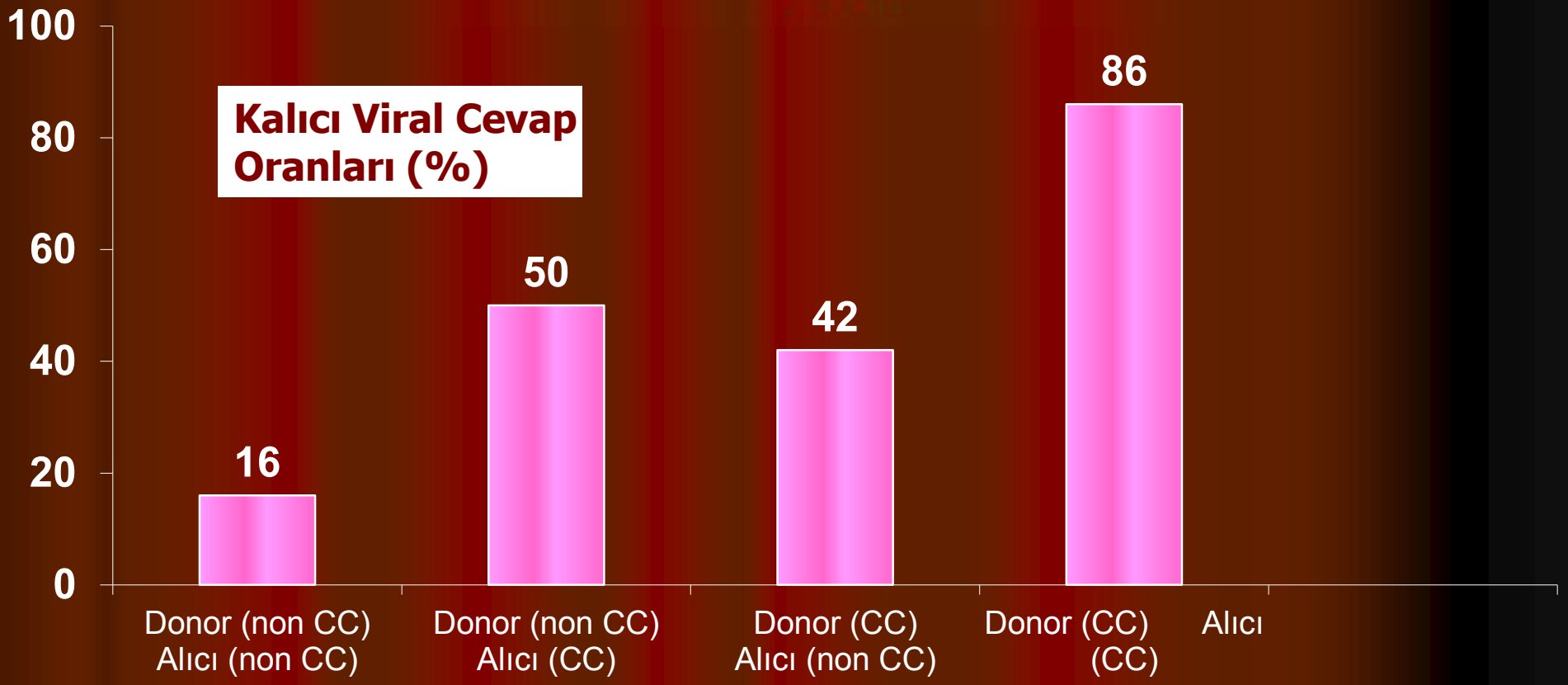
(hepatitis B virus, hepatocellular carcinoma)

Kullanılan immunsupresyonun tipi ve dozu

Akut rejeksiyon ve pulse steroid tedavisi sayısı


IL28B Genotype and Response to Antiviral Therapy
(%)
60
40
20
0
16
56
42
58
donor (non-CC) / recipient (non-CC)
N=19
donor (CC) / recipient (non-CC)
N=22
N=12
Donor : Recipient IL28B genotype

IL28b genotipi ve PEG+Riba tedavisi sonrası kalıcı virolojik cevap



Karaciğer Nakli Sonrası HCV Tedavisi

- Çok merkezli çalişma
  - GT1 HCV
  - ≥ F2 (n = 20) veya kolestatik hepatit (n = 8)
  - Peg/R lead-in 4 hf, sonra, BOC 800 mg TID + Peg/R (n = 17)
  - TVR lead-in (n = 5)

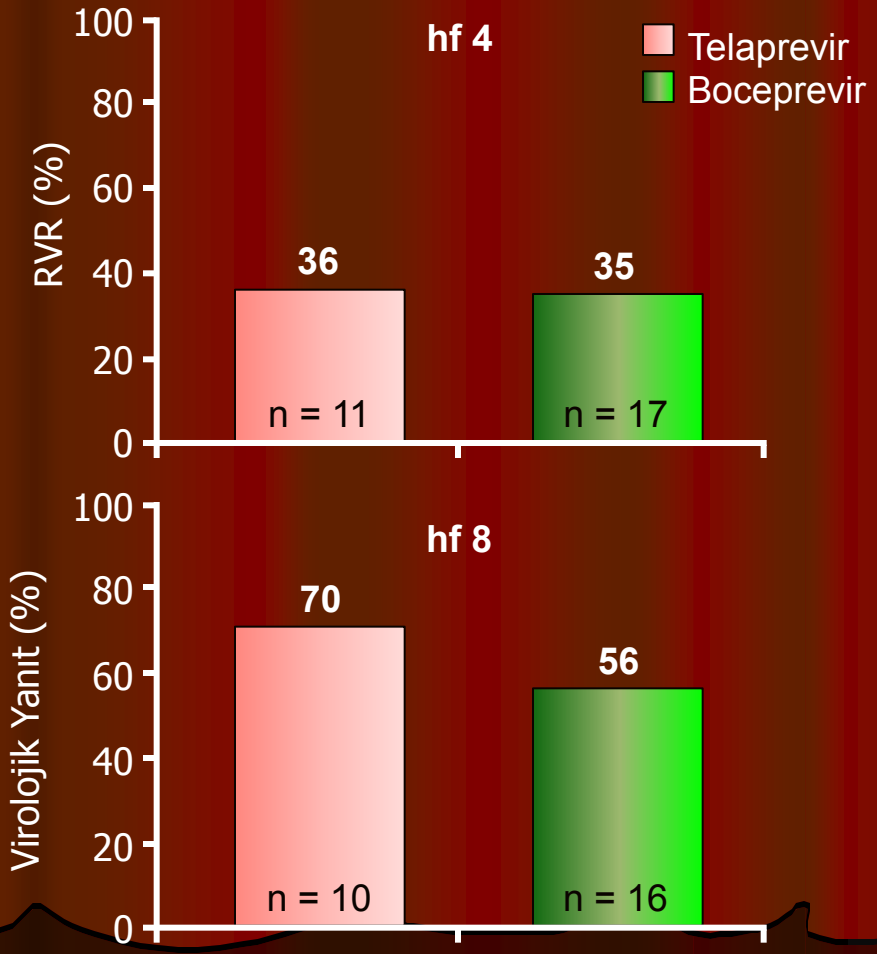
    Peg/R lead-in 4 hf, sonra TVR 750 mg TID + Peg/R
  - TVR lead-in yapmadan(n = 6)
    - TVR 750 mg TID + Peg/R

Characteristic	BOC + P/R (n = 17)	TVR + P/R (n = 11)
Fibrosis stage ≥ F3, %	53	55
Cholestatic hepatitis, %	24	36
Cyclosporine, %	65	45
Tacrolimus, %	35	55
Mycophenolate mofetil, %	41	27
HCV RNA, log_{10} IU/mL (range)	7.0 (5.9-8.5)	7.1 (5.2-8.3)
ALT*, IU/L	191	99
Total bilirubin, µmol/L	52	47
CrCl, mL/min	83	73
Neutrophil count, cells/mm^3	2900	2100
Platelet count, cells/mm^3	142,000	145,000

P = .01

Coilly A, et al. EASL 2012. Abstract 47.

Karaciğer Nakli Sonrası HCV Tedavisi



- Anemi: en sık yan etki
  - BOC: %71 ; TVR: %55
  - > %90 hastada EPO ihtiyacı
- TVR grubunda 1 ölüm

- Calcineurin inhibitor dozları
  - BOC grubu
    - Cyclosporine dozu ↓ 1.3-kat
    - Tacrolimus dose ↓ 5.0-kat
  - TVR group
    - Cyclosporine dozu ↓ 4-kat
    - Tacrolimus dozu ↓ 35-kat

Coilly A, et al. EASL 2012. Abstract 47.

Liver Transpl. 2012 Sep;18(9):1053-9. doi: 10.1002/lt.23482.

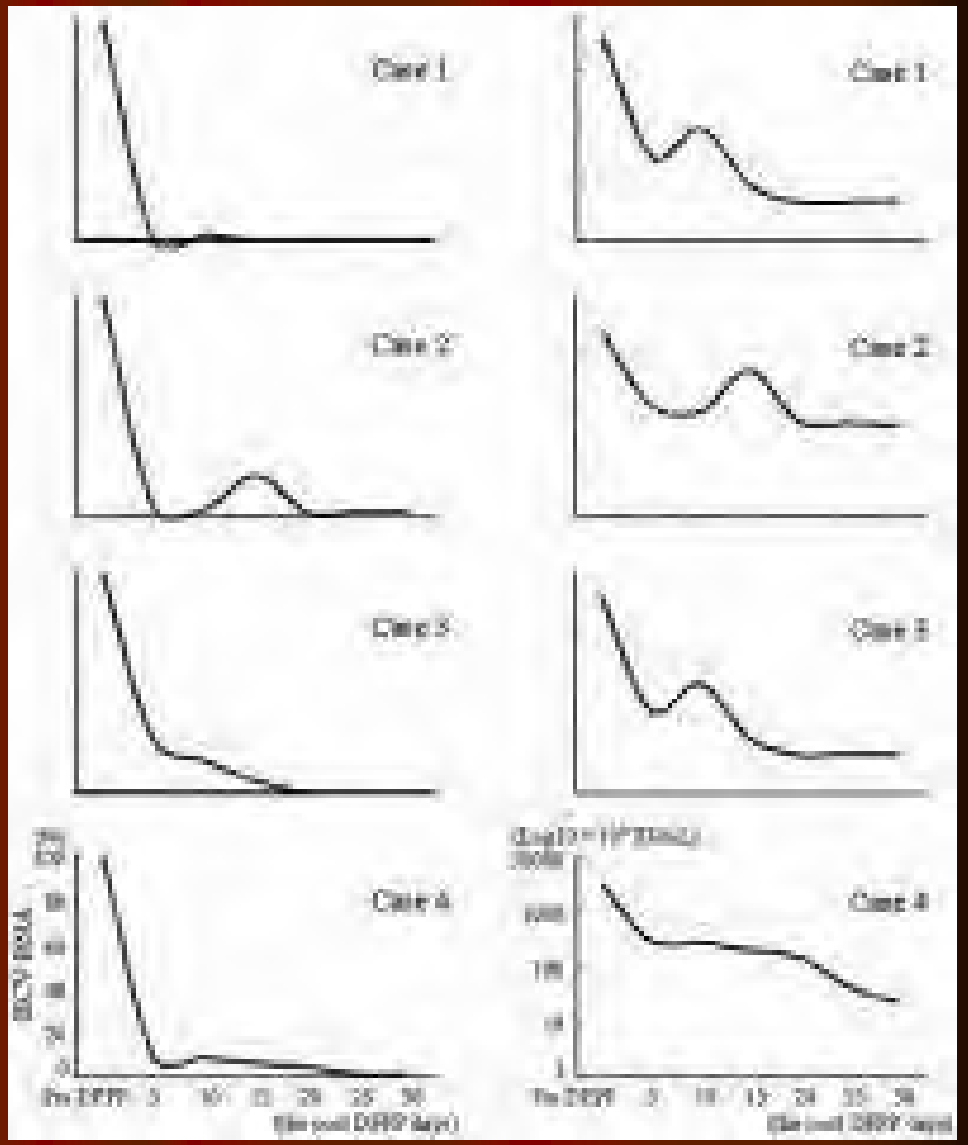
Case report of successful peginterferon, ribavirin, and daclatasvir therapy for recurrent cholestatic hepatitis C after liver retransplantation.

Fontana RJ, Hughes EA, Appelman H, Hindes R, Dimitrova D, Bifano M.

Abstract

A recurrent hepatitis C virus (HCV) infection after liver transplantation (LT) can lead to accelerated allograft injury and fibrosis. The aim of this article is to report the first ever use of daclatasvir (DCV; also known as BMS-790052), a potent orally administered nonstructural 5A replication complex inhibitor, in combination with peginterferon α (PEG-IFNα) and ribavirin in an LT recipient. A 49-year-old female developed a severe recurrent HCV genotype 1b infection 4 months after transplantation with severe cholestasis on biopsy, an HCV RNA level of 10,000,000 IU/mL, an alkaline phosphatase level of 1525 IU/mL, and a total bilirubin level of 8.4 mg/dL. Despite partial virological suppression with PEG-IFNα and ribavirin, progressive allograft failure ensued and culminated in retransplantation at 9 months. Three months after the second transplant, DCV (20 mg/day), PEG-IFNα2a (180 μg/week), and ribavirin (800 mg/day) were prescribed for early recurrent cholestatic HCV. Serum HCV RNA became undetectable at week 3 of treatment and remained undetectable during 24 weeks of triple therapy and during the posttreatment follow-up. DCV was well tolerated, and the trough drug levels were within the targeted range throughout the treatment. The cyclosporine trough levels were also stable during and after therapy. In conclusion, the lack of anticipated drug-drug interactions between DCV and calcineurin inhibitors and the potent antiviral efficacy of DCV make this agent (in combination with PEG-IFN and ribavirin) an attractive antiviral regimen worthy of further study in LT recipients with recurrent HCV.

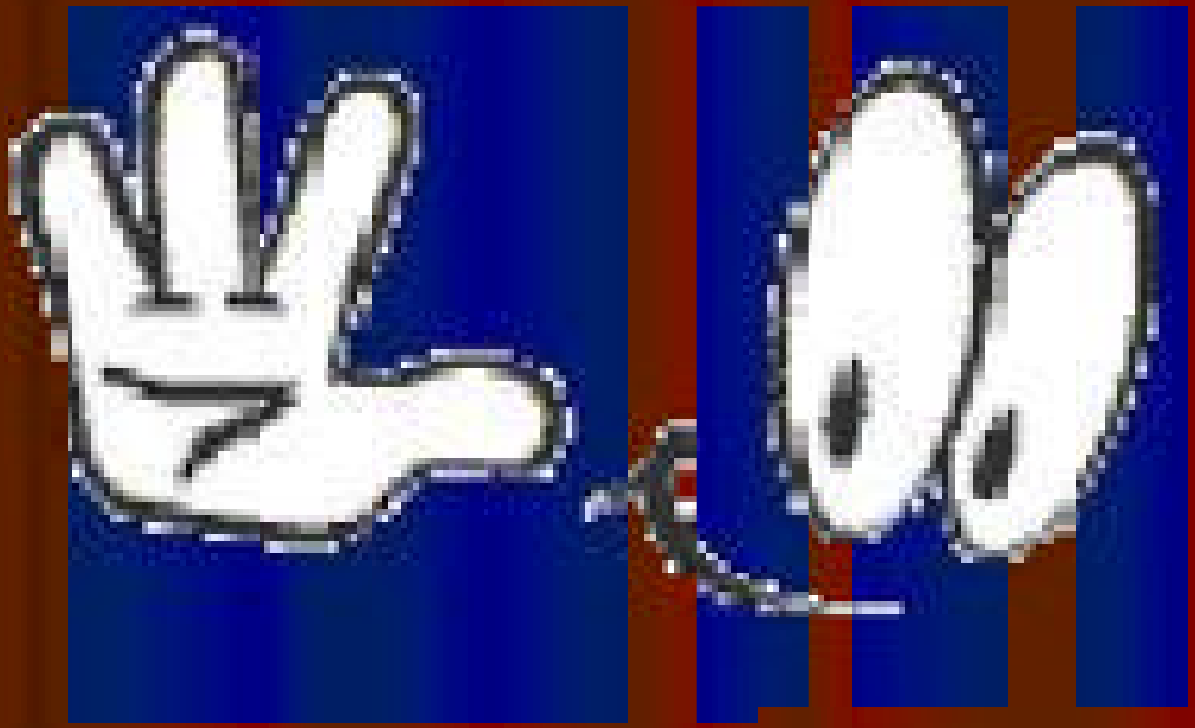
The dynamics of HCV RNA level in each patient within 30 days after the DFPP treatment.



Taniguchi M, et al. Impact of double-filtration plasmapheresis in combination with interferon and ribavirin in living donor liver transplant recipients with hepatitis C. Transplantation 2006.

Future aims: Prevention of re-infection

Direct inhibition of HCV replication by i.v. silibinin

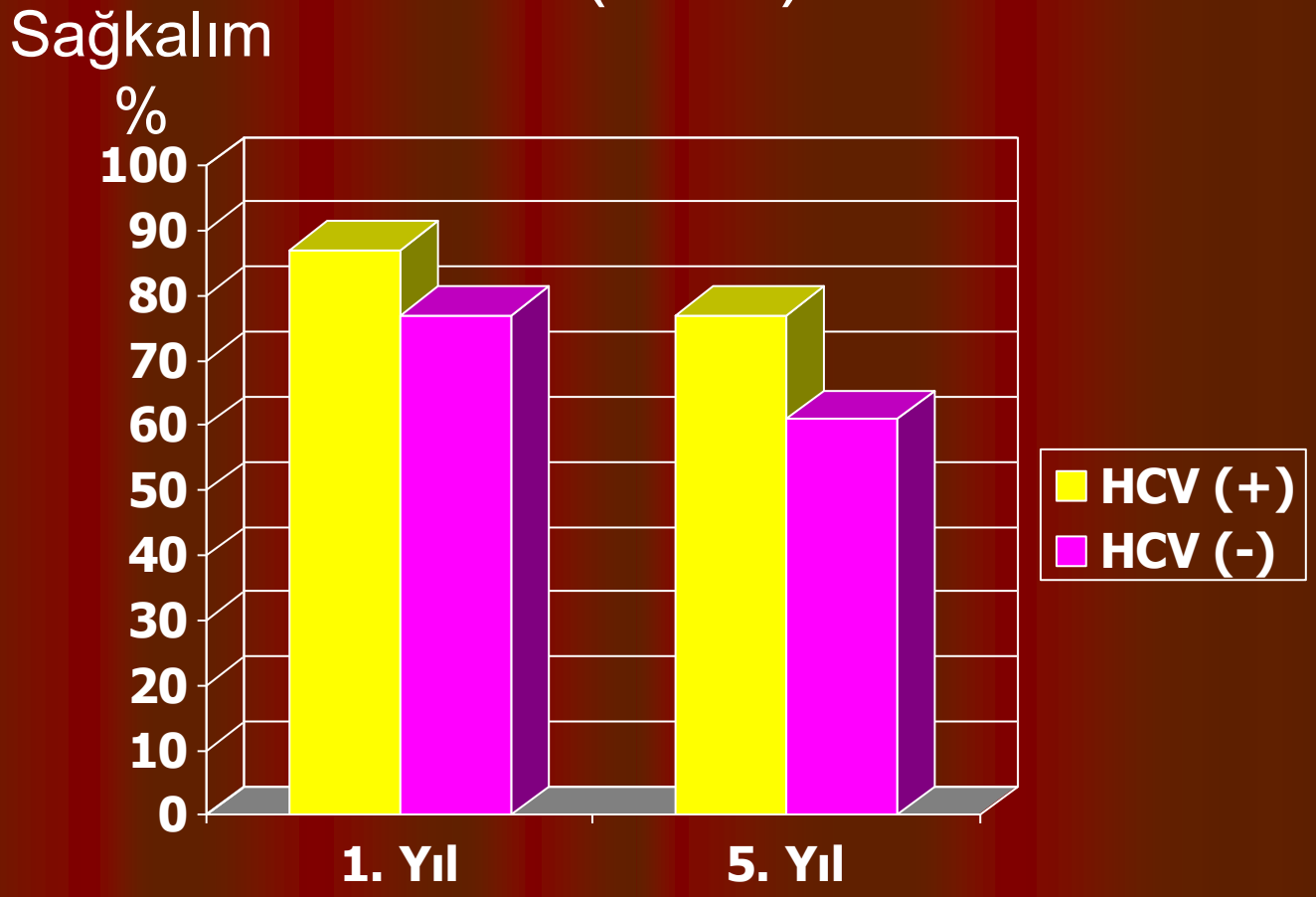


Teşekkürler

İmmunosupresiflerin etkisi

- ✓Akut rejeksiyon tedavisi için verilen her bir bolus steroid HCV RNA değerinde 1 log artışa yol açar.
- ✓Olumsuz etkisi en fazla olan OKT3.
- ✓Cyclosporine ve Tacrolimus'un viral replikasyon üzerine etkisi gösterilememiş.
- ✓Mycophenylate mofitil ve Rapamycin hakkındaki bilgiler çelişkili
- ✓"IL2-receptor monoclonal antibody" (Basiliximab, daclizumab) viral yükü arttırır

522 hasta
283 (54%) HCV



Berenguer M. Hepatology. 2002

HCV: RUTİN BİOPSİ

Histoloji ağır ise prognoz kötü

Berenguer M, Lake J 2005
Biggins SW, Terrault NA Infect Dİs Clin N Am 2006

PROGNOZ GÖSTERGELERİ

Postop 1. Yıl biopsi

Hepatit bulguları

Hafif Orta /ağır

<% 10 Siroz gelişme riski >%65

PROGNOZ GÖSTERGELERİ

Postop 1. Yıl biopsi

Hepatit bulguları	Siroz riski
Hafif	<% 10
Orta /ağır	>%65

- Polyclonal HCIG *(Davis Liver Transplant 2005)*
  - HCIG 75 mg/kg 14 hafta
  - HCIG 200 mg/Kg 14 hafta
  - Placebo
    - HCV RNA'ya etkisi yok

- Monoclonal HCV AbXTL 68 *(Schiano Liver Transplant 2006)*
  - 2. Gün HCV RNA azalması
  - 240 mg: -2.4 log
  - Placebo: -1.5 log
    - 7. Gün fark yok (anti-E2'de anlamlı artış)

Kalıcı virolojik yanıt sonrası:

2. Yılda % 35
5. Yılda % 20
Hastada “Fibrozis” ilerlemeye devam etmiş.

Abdelmalek MF, *et al.* Sustained viral response to interferon and ribavirin in liver transplant recipients with recurrent hepatitis C. *Liver Transpl.* 2004

% 18

Bizollon T, et al. Benefit of sustained virological response to combination therapy on graft survival of liver transplanted patients with recurrent chronic hepatitis C. Am. J. Transplant. 2005

Table 2: Change in activity score and fibrosis score at the end of follow-up (METAVIR score)

	Nonresponders (n = 46)	Responders (n = 34)	p
Necrotico-inflammatory activity			<0.001
Improvement	7 (15%)	21 (62%)	
No change	15 (33%)	10 (29%)	
Worsening	24 (52%)	3 (9%)	
Fibrosis			<0.001
Improvement	0	13 (38%)	
No change	12 (26%)	15 (44%)	
Worsening	34 (74%)	6 (18%)	

Takip süresi (ortanca) : 57 ay 52 ay

Bizollon AJT 2005

Auto(Allo)immune Hepatitis

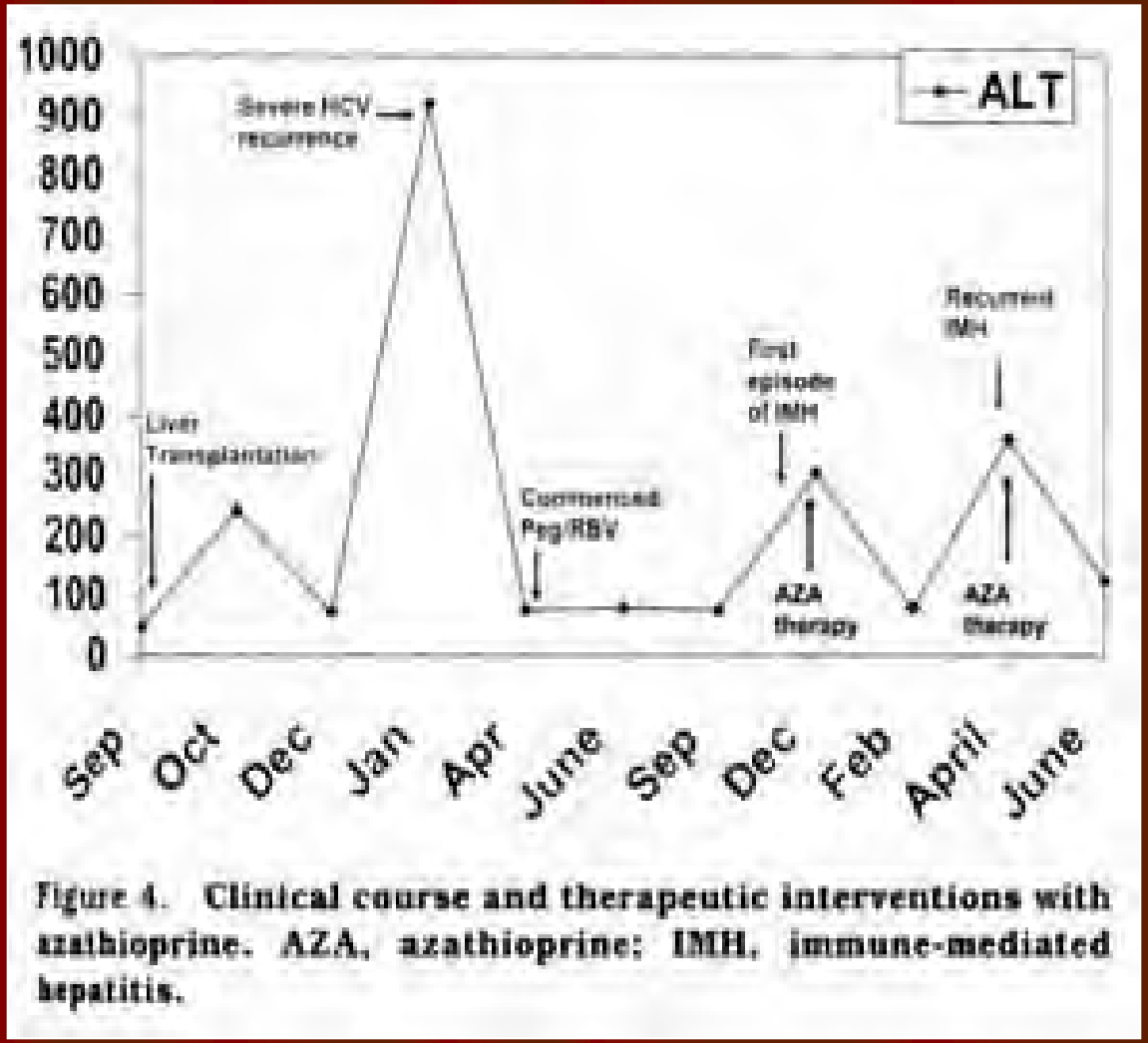


Figure 4. Clinical course and therapeutic interventions with azathioprine. AZA, azathioprine; IMH, immune-mediated hepatitis.

44 hasta: PEG IFN + Ribavirin

9

"probable" autoimmune hepatitis

Andreone. *Gut* 2007

Survival Without Cirrhosis In HCV+ve Liver Transplant PatientsWith or Without SVR

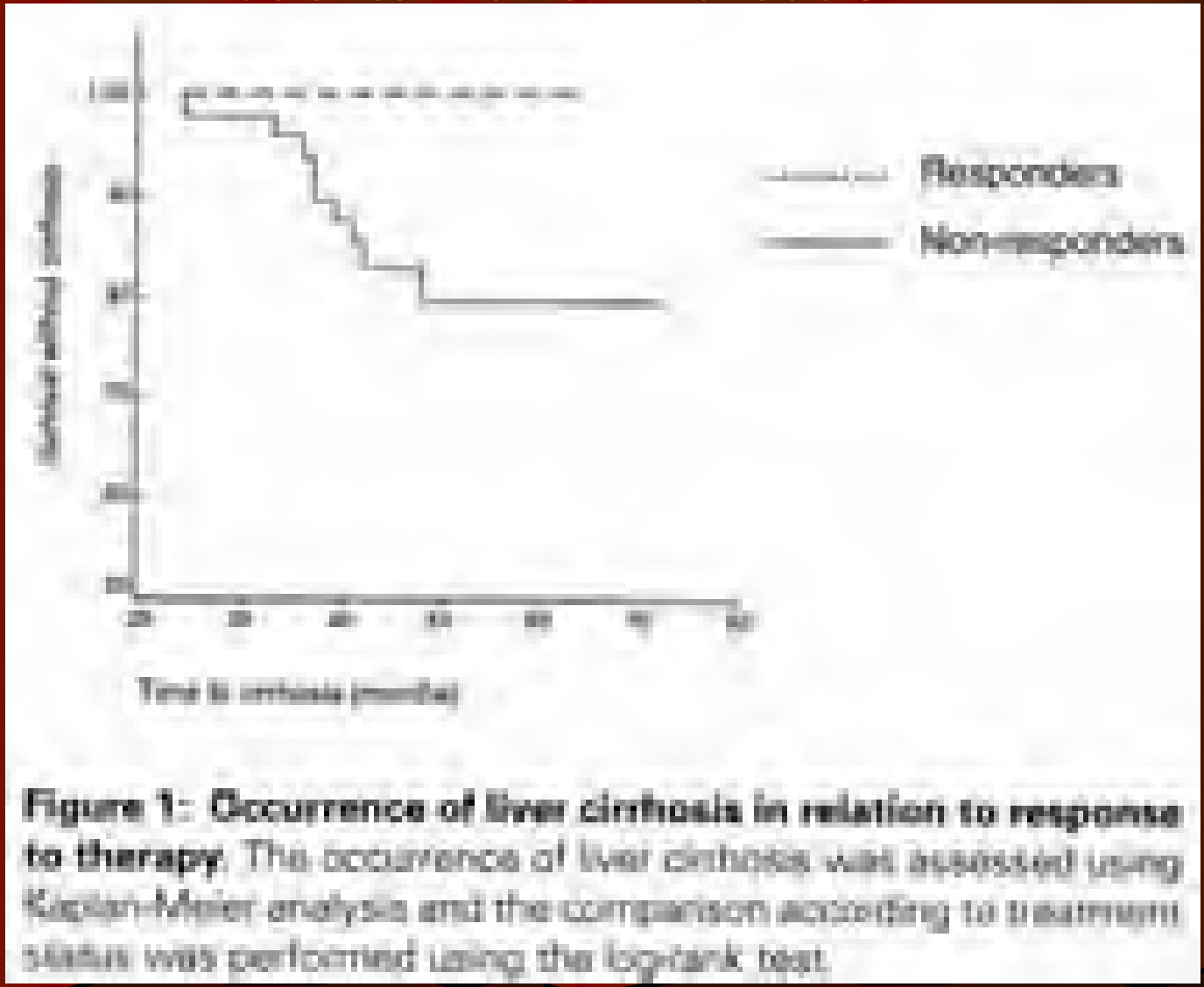


Figure 1: Occurrence of liver cirrhosis in relation to response to therapy. The occurrence of liver cirrhosis was assessed using Kaplan-Meier analysis and the comparison according to treatment status was performed using the log-rank test.

Bizollon AJT 2005; 6: 449-458

Yüksek Doz Steroid

- HCV RNA artar X 4-100
- Histolojik Progresyon çok daha hızlı
- Hasta ve Graft Sağkalımları düşer

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