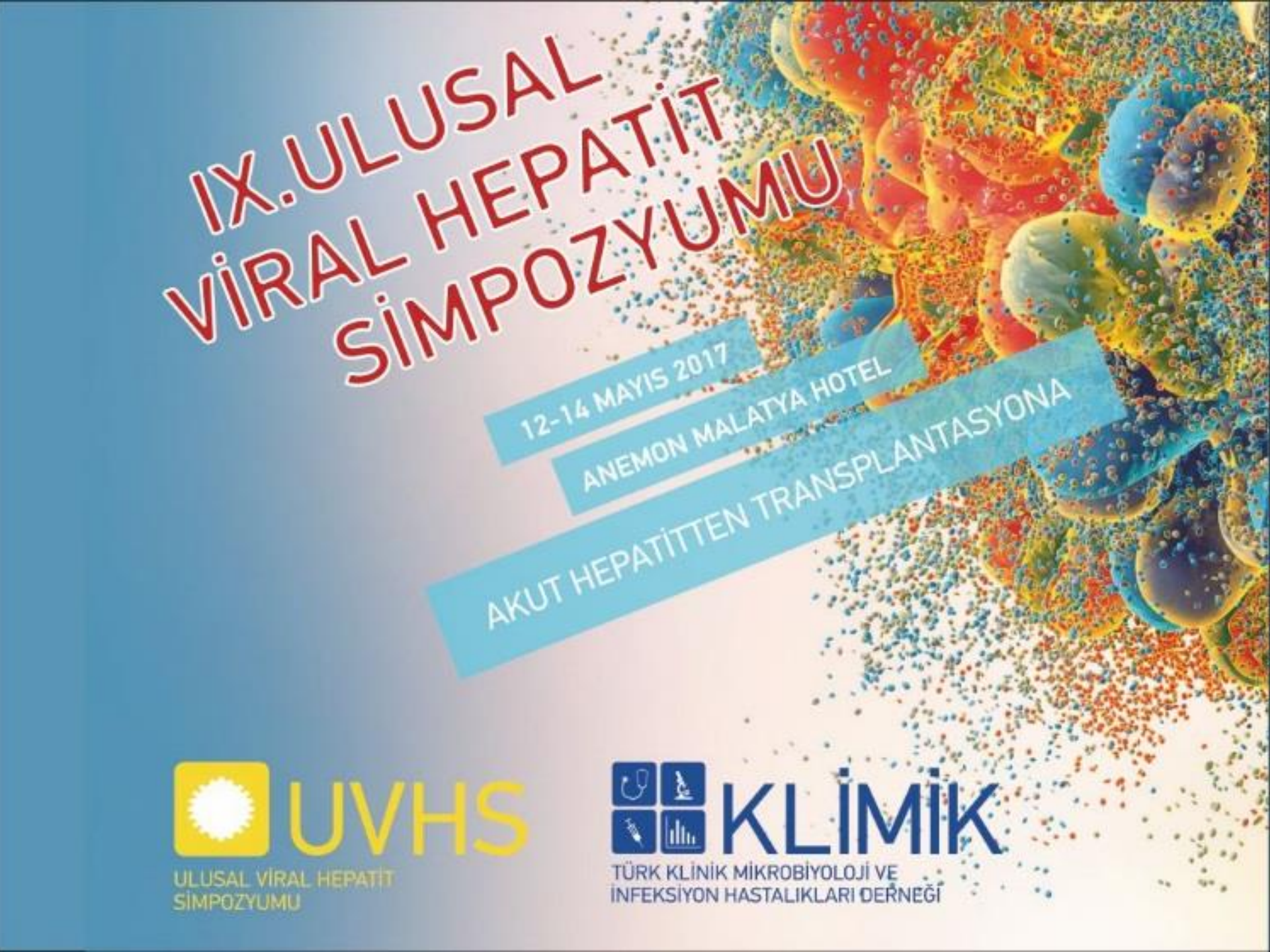

IX.ULUSAL
VİRAL HEPATİT
SİMPOZYUMU
12-14 MAYIS 2017
ANEMON MALATYA HOTEL
AKUT HEPATİTTEN TRANSPLANTASYONA
UVHS
ULUSAL VİRAL HEPATİT
SİMPOZYUMU
KLİMİK
TÜRK KLİNİK MİKROBİYOLOJİ VE
İNFEKSİYON HASTALIKLARI DERNEĞİ

Olgu Sunumu

Dr. Işıl Deniz Alıravcı
Ordu Üniversitesi Eğitim ve Araştırma Hastanesi
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği

OLGU

- 19.11.2014 ‘te poliklinikten başvuran erkek hasta
- 65 yaş, 63 kg
- Şik: Karın ağrısı
- Özgeçmiş: 22 yaşında sarılık geçirme
- Ek hastalık: 1974 yılında geçirilmiş akciğer Tbc, HT
- Sigara: son 30 yıldır kullanmıyor
- Alkol kullanımı yok
- Operasyon, diş tedavi öyküsü yok

Laborotuvar (ilk başvuru)

- **HBs Ag (+)**, Anti HBs (-), HBs Ag: 286 IU/ml
- Anti Hbc Ig M (-), Anti Hbc Ig G (+)
- Hbe Ag (+), Anti Hbe (+)
- **Anti HCV (+)**, Anti HAV Ig G (+)
- Anti HIV (-)
- **HBV DNA: 3.4X10^6 IU/ml, HBV Genotip D**
- **HCV RNA: 2.2x10^4 IU/ml, HCV Genotip 1b**

19.11.2014

Laborotuvar (ilk başvuru)

- AST: 176 U/L
- ALT: 231 U/L
- ALP: 145 U/L
- GGT: 229 U/L
- AFP: 58
- T bil: 1.8
- Direk bil: 1

- Wbc: 9800/mm^3
- Hgb: 15.6 mg/dl
- **Plt: 139000/mm^3**
- Pt: 15.1
- Aptt: 29.3
- INR: 1.3

19 Kasım 2014

Radyoloji ve Patoloji

- Özofago-gastro-duodenoskopi raporu: **Grade 1 özofagus varisleri, portal hipertansif gastropati**

- Kontrastlı Toraks Tomografi: Sol akciğer apikoposterior pleroparankimal kalınlaşmalar, parankimal düzensiz kalsifikasyonlar, plevral kasifik kalınlaşma, milimetrik subplevral kalsifik nodül

- Üst abdomen MR: En büyüğü sağda 13 mm, solda 17 mm olmak üzere her iki böbrekte kontrastlanmanın izlenmediği kortikal basit kistler

- **Karaciğer Biyopsi: HAİ: 7/18 F: 3/6**

Table 3. Approved HCV drugs in the European Union in 2015.

Product	Presentation	Posology
PegIFN-α2a	Solution for injection containing 180, 135 or 90 µg of Peg	Once weekly subcutaneous injection of 180 µg reduction needed)
PegIFN-α2b	Solu Peg	ubcutaneous injection of 1.5 µg/ ose reduction needed)
Ribavirin	Cap	in the morning and 3 in the evening if body weight <75 kg or and 3 in the
Sofosbuvir		g)
Simeprevir		ing)
Daclatasvir		g)
Sofosbuvir/ledipasvir	Tablets containing 400 mg of sofosbuvir and 90 mg of ledipasvir	One tablet once daily (morning)
Paritaprevir/ombitasvir/ ritonavir	Tablets containing 75 mg of paritaprevir, 12.5 mg of ombitasvir and 50 mg of ritonavir	Two tablets once daily (morning)
Dasabuvir	Tablets containing 250 mg of dasabuvir	One tablet twice daily (morning and evening)

Sofosbuvir +ledipasvir
temin edilemedi

Tenofovir
Peg IFN 2b 100 mg
Ribavirin 1000 mg

Klinik Seyir

- IFN/RBV-İlişkili Hematolojik Yan Etkiler

  Nötropeni
  Trombositopeni
  Anemi

Yan Etkiler

Trombositopeni (60.000)

Halsizlik, eklem ağrısı

- **9 AY TENOFOVİRLE MONOTERAPİYE DEVAM EDİLİYOR**

17 Nisan 2015

Laborotuvar

Tedavi başlangıcı

	WBC	HBG	PLT	AST	ALT	ALP	GGT
19.03.2015	5100	14.6	120.000	123	112	204	278
30.03.2015	3500	13.1	**60.000**	142	105		
17.04.2015	8000	14.2	127.000	90	84	176	169

Tedavi kesiliyor

Laborotuvar

- **9 AY TENOFOVİR MONOTERAPİSİ ALTINDAKİ LABOROTUVAR DEĞERLERİ**

	AST	ALT	ALP	GGT	T.BİL/D. BİL	AFP	Hbe Ag	Anti Hbe Ag	HBV DNA
Tenofovir 1. ay	90	84	176	169	1 / 0.6	86	borderline	+	1.2x10^3
Tenofovir 3. ay	79	71	203	254	0.7 / 0.5	72			1.7X10^2
Tenofovir 6. ay	64	53	114	134	0.9 / 0.6	66	-	+	NEGATİF
Tenofovir 9. ay	57	51	113	106					

HCV tedavisinde köşe taşları

FDA Onayları

1991 IFN alfa-2b

1996 IFN alfa-2a

1997 "consensus" IFN

1998 IFN alfa-2b ve Ribavirin

2001 PegIFN alfa-2b ve Ribavirin

2002 PegIFN alfa-2a ve Ribavirin

2011 DAA I (Boceprevir ve Telaprevir)

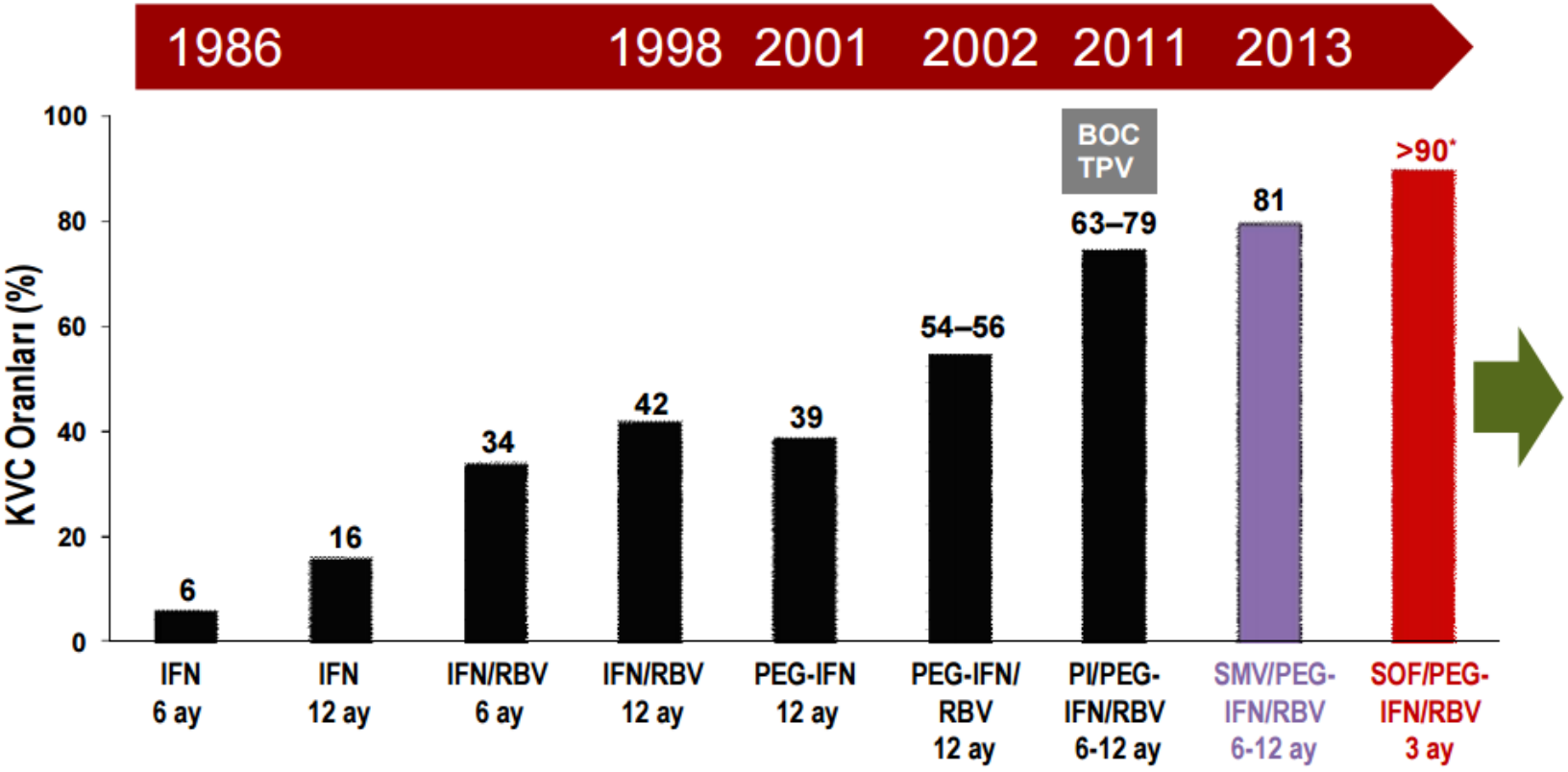
2013 DAA II (SOFOSBUVIR ve Simeprevir)

2014 **SOFOSBUVIR+Ledipasvir**

2014 **PARITAPREVIR+ritonavir+OMBITASVIR** ve **DASABUVIR (PrOD)**

2015 SOFOSBUVIR+DACLATASVIR

2015+ IFN'suz TEDAVİLER;DAHA ETKİLİ, DAHA KISA SÜRELİ



* NEUTRINO çalışması: GT1 hastalarda KVY 12 oranı %90 (12 hafta SOF+PEG-IFN+RBV)

Adapted from Strader DB, et al. Hepatology 2004;39:1147-71; INCIVEK [PI]. Cambridge, MA: Vertex Pharmaceuticals, 2013; VICTRELIS [PI]. Whitehouse Station, NJ: Merck & Co, 2014; Jacobson I, et al. EASL 2013. Amsterdam. Poster #1425; Manns M, et al. EASL 2013. Amsterdam. The Netherlands. Oral #1413; Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02.

HepAtölye III: Hepatit C Virusu İnfeksiyonunun Tedavisinde Yeni Antiviraller (4-6 Aralık 2015, İstanbul)'in Ardından

After a Workshop on the Novel Antivirals for Treatment of Hepatitis C Virus Infection (4-6 December 2015, İstanbul)

Süda Tekin[1], Bilgehan Aygen[2], Mehtap Aydın[3], Funda Şimşek[4], HepAtölye III Düzenleme Kurulu

Tablo 6. Hepatit C Virusu Genotip 1 veya 4 İnfeksiyonu Olan Sirotik Olmayan Tedavi Naif veya PegIFN + RBV Deneyimli Hastalarda Tedavi Önerileri*

	HCV Genotip		
	1a	1b	4
SOF + PegIFN/RBV	12 hafta		12 hafta
SMV + PegIFN/RBV	12 hafta (naif veya relaps) 24 hafta (parsiyel/ "null")		12 hafta (naif veya relaps) 24 hafta (parsiyel/ "null")
LDV/SOF	8-12 hafta†		12 hafta
OBV/PTV-RTV + DSV	12 hafta (+ RBV)	12 hafta	Önerilmiyor
OBV/PTV-RTV	Önerilmiyor		12 hafta (+ RBV)
SOF + SMV	12 hafta		12 hafta
SOF + DCV	12 hafta		12 hafta

*Kaynak 13 ve 14'ten uyarlanmıştır. †Tedavi naif, sirotik olmayan ve bazal HCV RNA düzeyi < 6 milyon İÜ/ml olan hastalarda 8 hafta verilebilir (özellikle F3 fibroz hastalarında). PegIFN: Pegile interferon, RBV: Ribavirin, LDV: Ledipasvir, SOF: Sofosbuvir, OBV: Ombitasvir, PTV: Paritaprevir, RTV: Ritonavir, DSV: Dasabuvir, SMV: Simeprevir, DCV: Daklatasvir.

Initial Treatment Box. Summary of Recommendations for Patients Who are Initiating Therapy for HCV Infection or Who Experienced Relapse after Prior PEG/RBV Therapy, by HCV Genotype

Genotype	Recommended	Alternative	NOT Recommended
1	**IFN eligible:** SOF + PEG/RBV x 12 weeks **IFN ineligible:** SOF + SMV ± RBV x 12 weeks	**IFN eligible:** SMV x 12 weeks + PEG/RBV x 24 weeks* **IFN ineligible:** SOF + RBV x 24 weeks	TVR + PEG/RBV x 24 or 48 weeks (RGT) BOC + PEG/RBV x 28 or 48 weeks (RGT) PEG/RBV x 48 weeks Monotherapy with PEG, RBV, or a DAA Do not treat decompensated cirrhosis with PEG or SMV
2	SOF + RBV x 12 weeks	None	PEG/RBV x 24 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR, BOC, or SMV
3	SOF + RBV x 24 weeks	SOF + PEG/RBV x 12 weeks	PEG/RBV x 24-48 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR, BOC, or SMV
4	**IFN eligible:** SOF + PEG/RBV x 12 weeks **IFN ineligible:** SOF + RBV x 24 weeks	SMV x 12 weeks + PEG/RBV x 24-48 weeks	PEG/RBV x 48 weeks Monotherapy with PEG, RBV, or a DAA Any regimen with TVR or BOC
5 or 6	SOF + PEG/RBV x 12 weeks	PEG/RBV x 48 weeks	Monotherapy with PEG, RBV, or a DAA Any regimen with TVR or BOC

Laborotuvar

- 15.12. 2015 ‘te (tenofovir tedavisinin 9. ayında) 3 ay süreyle Peg IFN-alfa 2b 100 mg + Ribavirin 1000 mg + Sofosbuvir 400 mg tedavisi başlandı.

	AST	ALT	ALP	GGT	T.BİL/D.BİL	AFP	HCV RNA
Tedavinin 1. ay	33	25	113	106	0.6/0.3	-	NEGATİF
Tedavinin 2. ay	32	24	-	90	0.8/0.2	-	NEGATİF
Tedavinin 3. ay	32	26	126	86	0.6/0.1	-	NEGATİF

	WBC	HGB	PLT
Tedavi öncesi 19.11.2015	6500	15.3	111.000
Tedavinin 1. haftası	**4000**	**15.3**	**64.000**
Tedavinin 1. ayı	3900	13.4	76.000
Tedavinin 2. ayı	3500	12.4	67.000
Tedavinin 3. ayı	**2400**	**11.4**	**62.000**
Tedavi sonu 1. ay	**5400**	**12**	**118.000**
Tedavi sonu 2. ay 05.05.2016	**4900**	**14**	**43.000**
16.08.2016	**11800**	**14.5**	**119.000**

Bir hafta sonra Peg IFN alfa 2b dozu 80 mg'a düşürülüyor

HCV RNA: + Hepatit C nüks 07.04.2016

?

Daru. 2017 Apr 20;25(1):11. doi: 10.1186/s40199-017-0177-x.

Combination of sofosbuvir, pegylated-interferon and ribavirin for treatment of hepatitis C virus genotype 1 infection: a systematic review and meta-analysis.

Dolatimehr F[1,2,3,4], Karimi-Sari H[1,2,3,4], Rezaee-Zavareh MS[1,2,3,4], Alavian SM[2,3,4], Behnava B[2,3,4], Gholami-Fesharaki M[5], Sharafi H[6,7,8].

Author information

Abstract

BACKGROUND: Hepatitis C virus (HCV) infection is an important cause of chronic liver disease which has been affected 3% of world's population. Some studies have shown that adding Sofosbuvir (SOF), an HCV polymerase inhibitor to the conventional therapy of Pegylated-interferon (PegIFN) plus Ribavirin (RBV) can increase the rate of sustained virologic response (SVR) among HCV-infected patients. This study was conducted to determine the effect of combination therapy with PegIFN and RBV plus SOF for chronic hepatitis C genotype 1 infection using systematic review with meta-analysis.

METHODS: In this study, electronic databases including PubMed, Scopus, Science Direct, and Web of Science were comprehensively searched using appropriate strategies containing all related keywords of "hepatitis C", "PegIFN", "RBV" and "SOF". Studies assessed the efficacy of combination therapy with PegIFN and RBV plus SOF for chronic hepatitis C genotype 1 infection were included in the meta-analysis.

RESULTS: After screening of 757 records, we included five articles with total sample size of 411 to the meta-analysis. Based on the fixed-effect model ($\chi^2 = 5.29$, $P = 0.26$ and $I^2 = 24.4\%$), pooled SVR rate for treatment regimen of PegIFN and RBV plus SOF was calculated as 88.54% (95% CI = 85.77%-91.32%).

CONCLUSIONS: Combination therapy with PegIFN and RBV plus SOF results in high treatment response in patients with HCV genotype 1 infection.

KEYWORDS: Hepatitis C; Meta-analysis; Pegylated-interferon; Ribavirin; Sofosbuvir

	AST	ALT	ALP	GGT	AFP	T.BİL/D.BİL	HBV DNA	HCV RNA
Tedavi sonu 1. ay	32	28	133	50	13	0.5/0.1	Negatif	5.6X10^5 IU/ML
Tedavi sonu 2. ay Hbs ag: 869	**96**	**64**	131	186		0.8/0.5		
Tedavi sonu 3. ay	**73**	**48**	146	199		0.8/0.5		

DİRENÇ BAKALIM MI??

Hepatit C nüks 07.04.2016

Öneriler

1. DEA ilaçlar asla tek başına kullanılmamalıdır.

2. Gü önce

Sofosbuvir/Peg-IFN/RBV tedavisinde

- Viral kırılma yok
- Tedavi başarısızlığı olan hastalarda direnç gösterilmemiş

Buti M et al. J Hepatol 2015;63:1511-1522

bir

ır. Bu

bilabileceği

göz önünde bu

Kronik Hepatit C Virusu İnfeksiyonunun Yönetimi: Türk Klinik Mikrobiyoloji ve İnfeksiyon Hastalıkları Derneği Viral Hepatit Çalışma Grubu Uzlaşı Raporu-2017 Güncellemesi

	AST	ALT	ALP	GGT	AFP	T.BİL/D.BİL	HBV DNA	HCV RNA
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Hepatit C nüks 07.04.2016

Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir 19.07.2016

Tablo 18. Daha Önce Kullanılan İlaç Rejimine ve HCV Genotipine Göre Yeniden Tedavi Önerileri

Daha Önceki Tedavi	Genotip	SOF/LDV	SOF/VEL	PTV-RTV/ OBV+DSV	PTV-RTV/ OBV	GRZ/EBV	SOF+DCV
SOF+RBV veya SOF+ PegIFN+ RBV	1	+RBV sirotik olmayan 12 hafta, sirotik 24 hafta	+RBV sirotik olmayan 12 hafta, sirotik 24 hafta	+RBV sirotik olmayan 12 hafta, sirotik 24 hafta	Hayır	+RBV sirotik olmayan ve HCV RNA ≤800 000 IU/ml olan 12 hafta; sirotik olmayan ve HCV RNA >800 000 IU/ml olan veya sirotik 24 hafta	+RBV siro olmayan hafta, siro 24 hafta
		hafta, sirotik 24 hafta	hafta, sirotik 24 hafta		olmayan 12 hafta, sirotik 24 hafta	HCV RNA ≤800 000 IU/ml olan 12 hafta; sirotik olmayan ve HCV RNA >800 000 IU/ml olan veya sirotik 24 hafta	hafta, siro 24 hafta
	5 veya 6	+RBV sirotik olmayan 12 hafta, sirotik 24 hafta	+RBV sirotik olmayan 12 hafta, sirotik 24 hafta	Hayır	Hayır	Hayır	+RBV siro olmayan hafta, siro 24 hafta

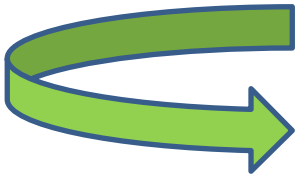
SUT'a göre Kr. Hepatit C Genotip 1b non sirotik ve kompanse sirotik Child Pugh A

tedavisinde Ombitasvir+Paritaprevir+Ritonavir+Dasabuvir ile 12 haftalık tedavi öneriliyor

Tedaviye uyumlu
Kendini iyi hissediyor
Bazen **kaşıntı** şik. var

		AST	ALT	ALP	GGT	T.BİL/D.BİL	HCV RNA
19.07.2016	Tenofovir + viekirax exviera	73	48	146	199	0.8/0.5	8.3 X10^5 IU/ML
16.08.2016	Tenofovir + viekirax exviera	18	11	115	50	**3.4/1.7**	**Negatif**
19.09.2016	Tenofovir + viekirax exviera	19	12	122	26	0.9/0.4	
17.10.2016	Tenofovir + viekirax exviera	21	13	147	24	0.6/0.2	**Negatif**

- Viekirax exviera ile 3 aylık tedavi bitimi hastanın kaşıntısı geçiyor
- Tedavi sonu 12.haftada HCV RNA negatif
- KVY elde edildi.
- Mayıs 2017



Hasta halen tenofovir kullanmakta
HBV DNA(-) , HCV RNA(-)

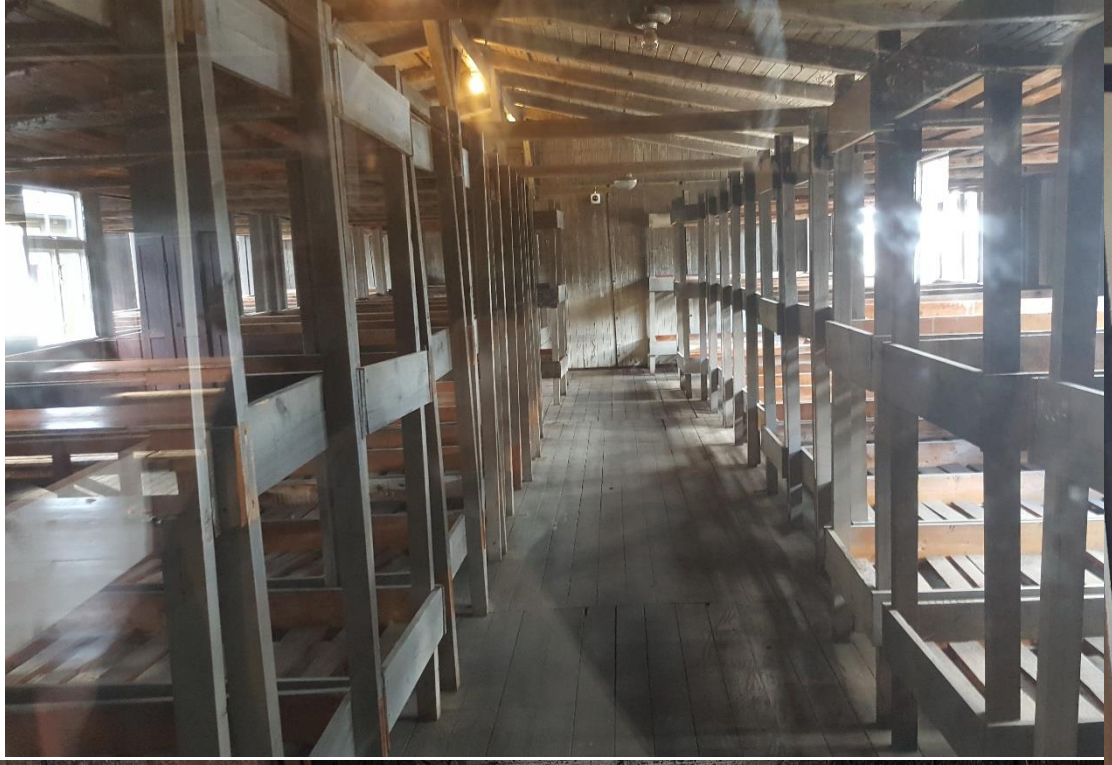
Laborotuvar (son başvuru)

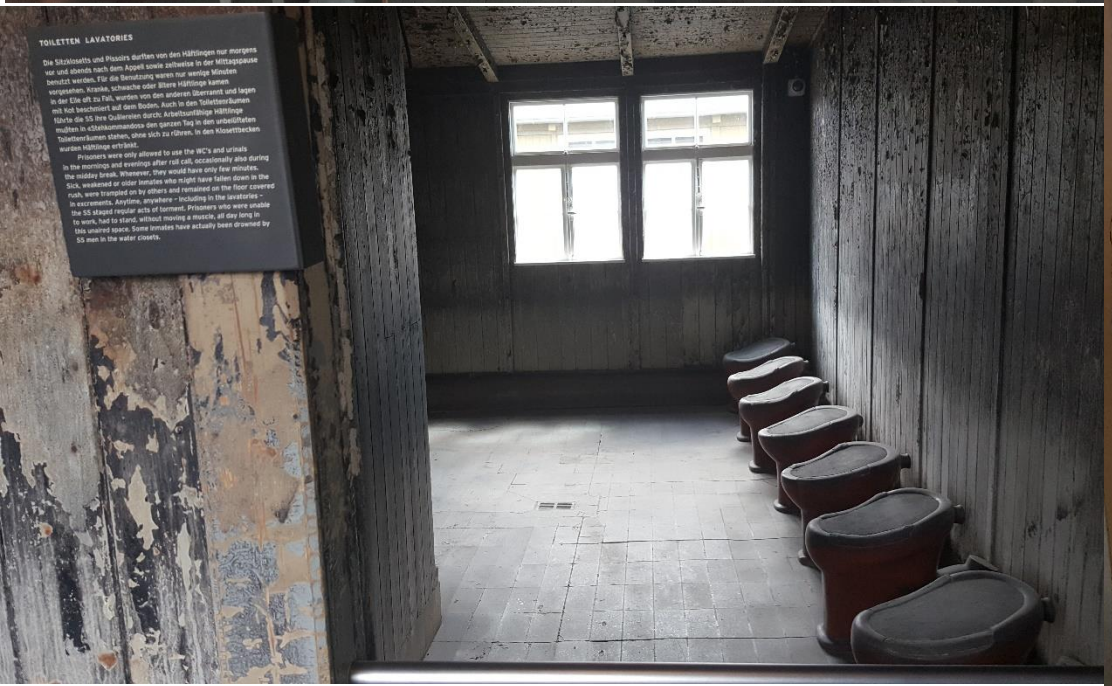
04.05.2017

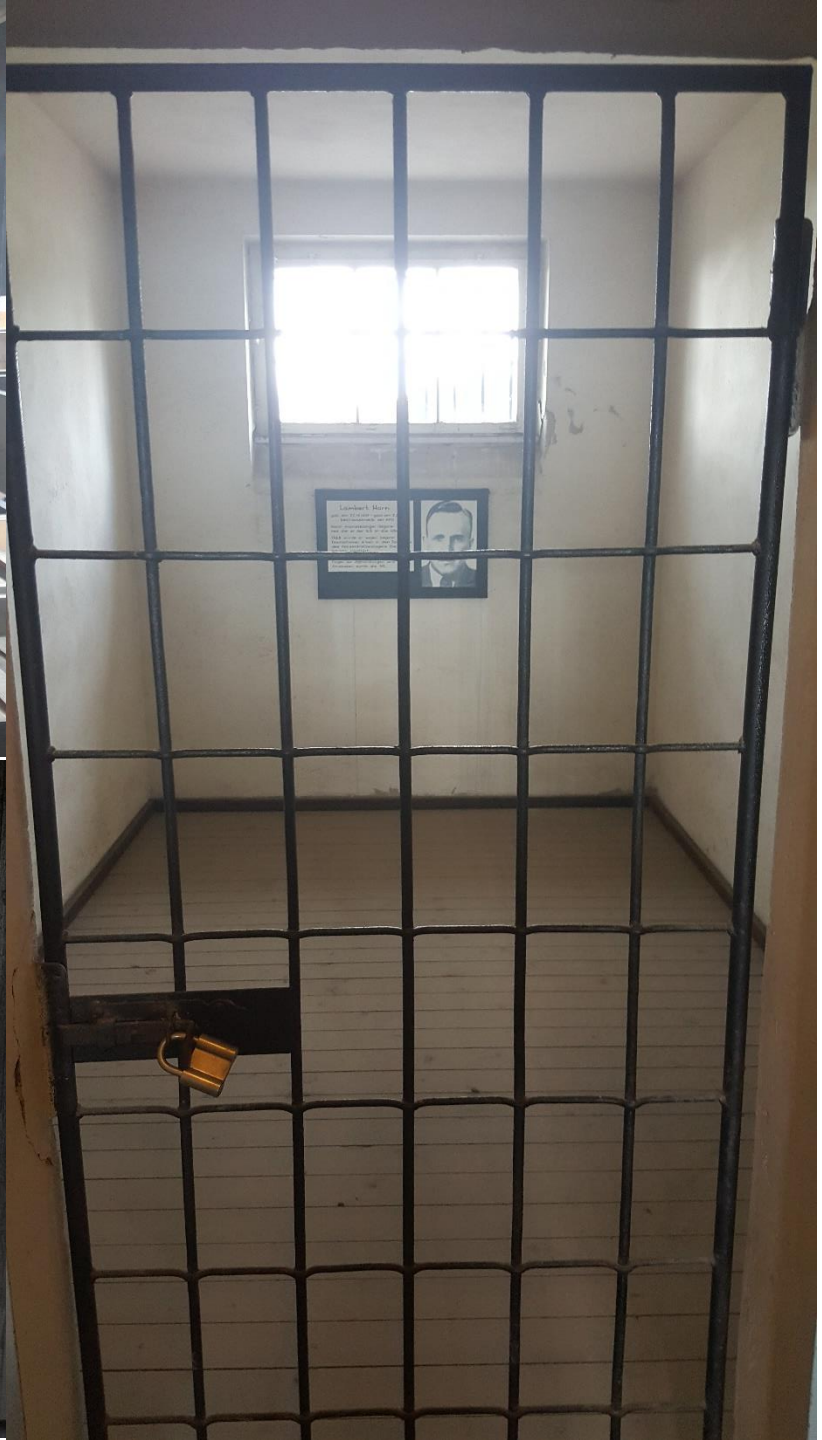
- **HBs Ag:1.16**
- Anti HBs: 0.88
- Wbc: 8080
- Hgb:14.8
- Plt: 146.000

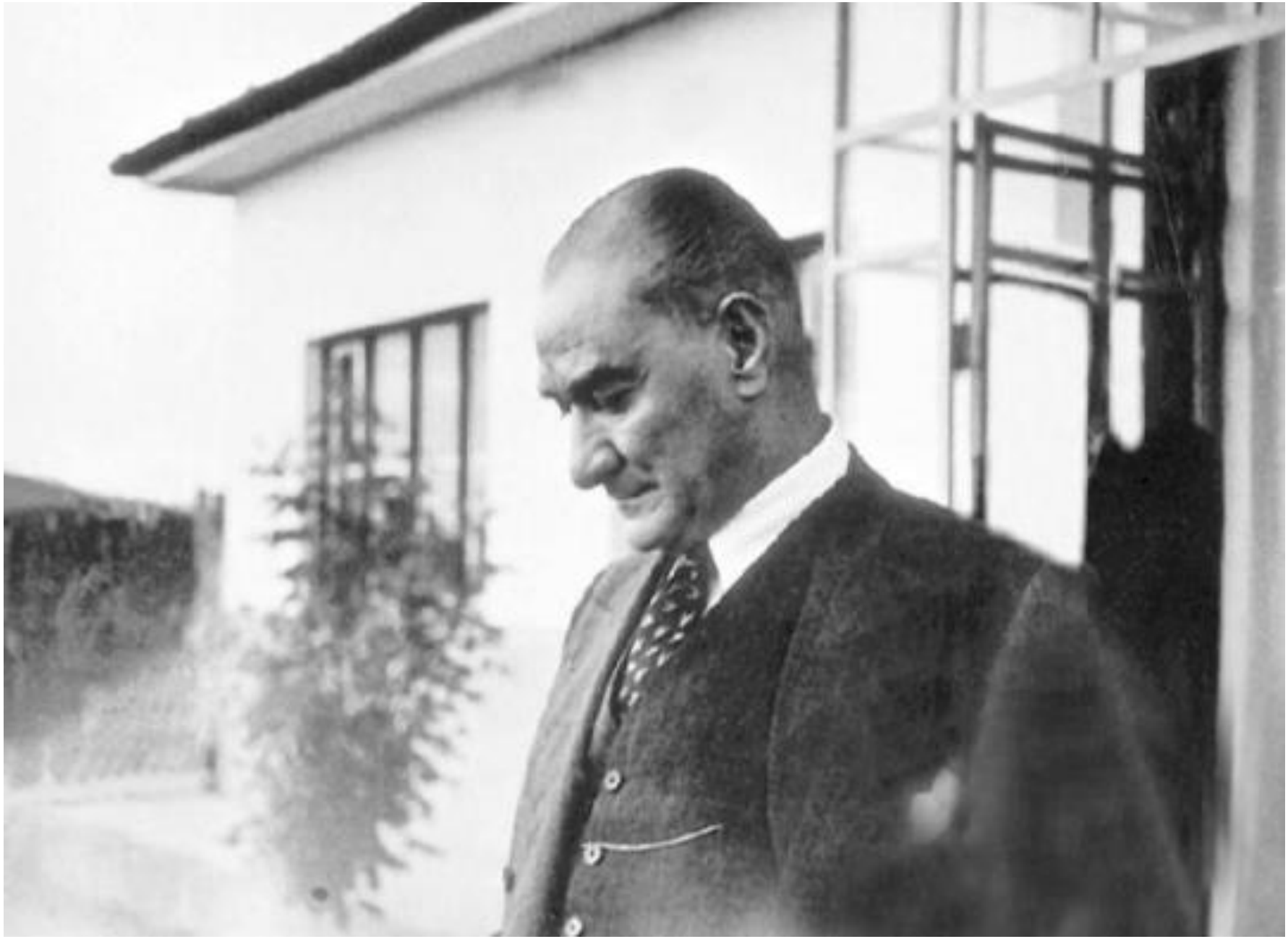
- AST:22
- ALT: 20
- AFP: 4.09
- T.p:7.6
- Alb:4.3
- BUN: 18.4
- Kreatn:1
- PT: 14.4 sn
- APTT: 27.9 sn
- INR: 1.04

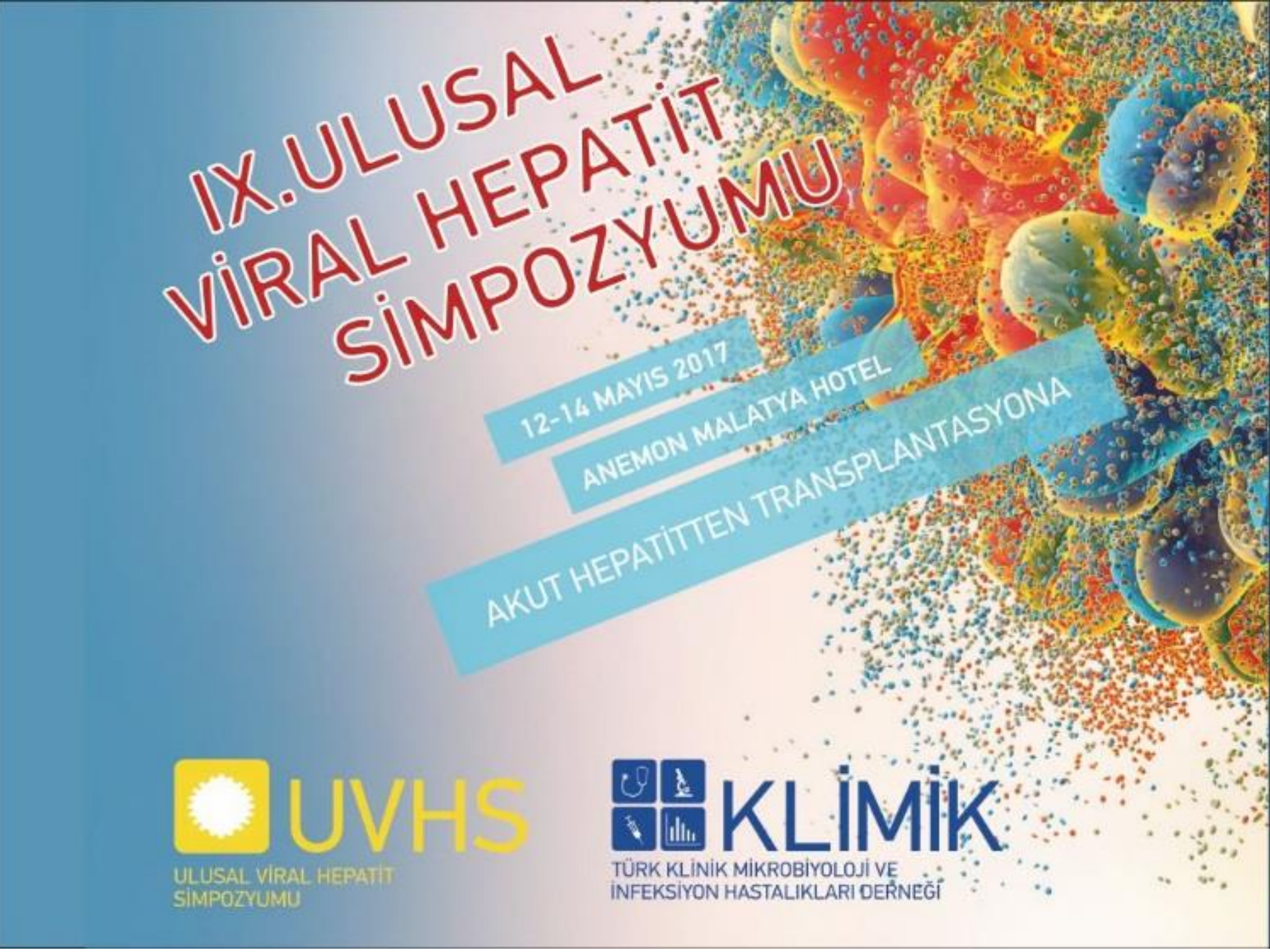
TEŞEKKÜRLER




TOILETTEN LAVATORIES
Die Sitzklosetts und Pissoirs durften von den Häftlingen nur morgens vor und abends nach dem Appell sowie zeitweise in der Mittagspause benutzt werden. Für die Benutzung waren nur wenige Minuten vorgesehen. Kranke, schwache oder ältere Häftlinge kamen in der Eile oft zu Fall, wurden von den anderen überrannt und lagen mit Kot beschmiert auf dem Boden. Auch in den Toilettenräumen führte die SS ihre Quälereien durch; Arbeitsunfähige Häftlinge mußten in «Strafkommandos» den ganzen Tag in den unbelüfteten Toilettenräumen stehen, ohne sich zu rühren. In den Klosettbecken wurden Häftlinge ertränkt.
Prisoners were only allowed to use the WC's and urinals in the mornings and evenings after roll call, occasionally also during the midday break. Whenever, they would have only few minutes. Sick, weakened or older inmates who might have fallen down in the rush, were trampled on by others and remained on the floor covered in excrements. Anytime, anywhere – including in the lavatories – the SS staged regular acts of torment. Prisoners who were unable to work, had to stand, without moving a muscle, all day long in this unaired space. Some inmates have actually been drowned by SS men in the water closets.


Lambert Horn

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TÜRK KLİNİK MİKROBİYOLOJİ VE
İNFEKSİYON HASTALIKLARI DERNEĞİ