DAA yeni ilaç çalışmaları ve beklentiler

Dr. Kenan Hızel

Günümüzde HCV tedavisi

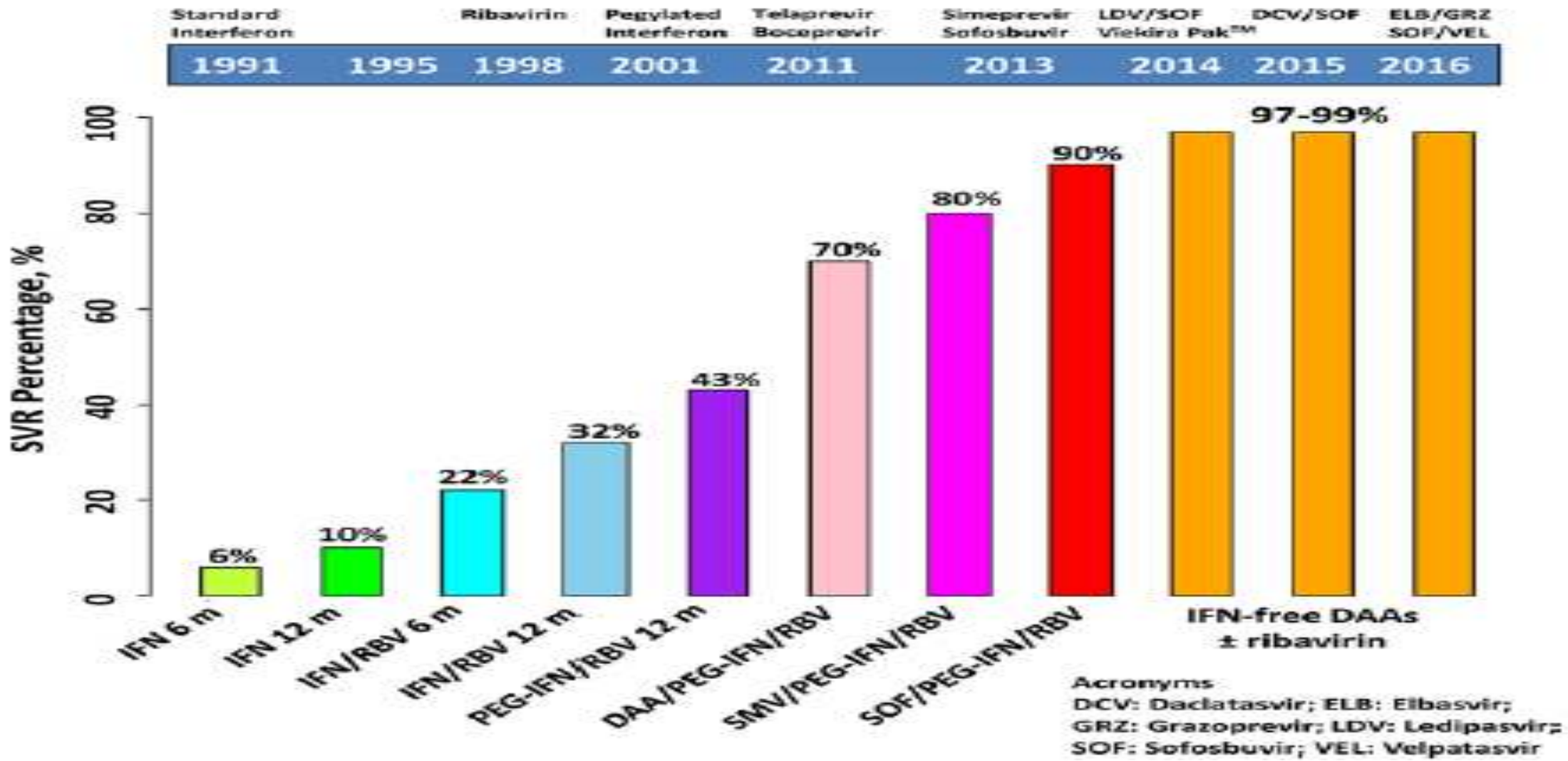
- Daklatasvir
- Elbasvir
- Grazoprevir
- Sofosbuvir
- Ledipasvir
- Ombitasvir
- Paritaprevir
- Ritonavir
- Simeprevir
- Velpatasvir

±

Ribavirin

(genotip, RAV olasılığı ve hastalığın dönemine göre)

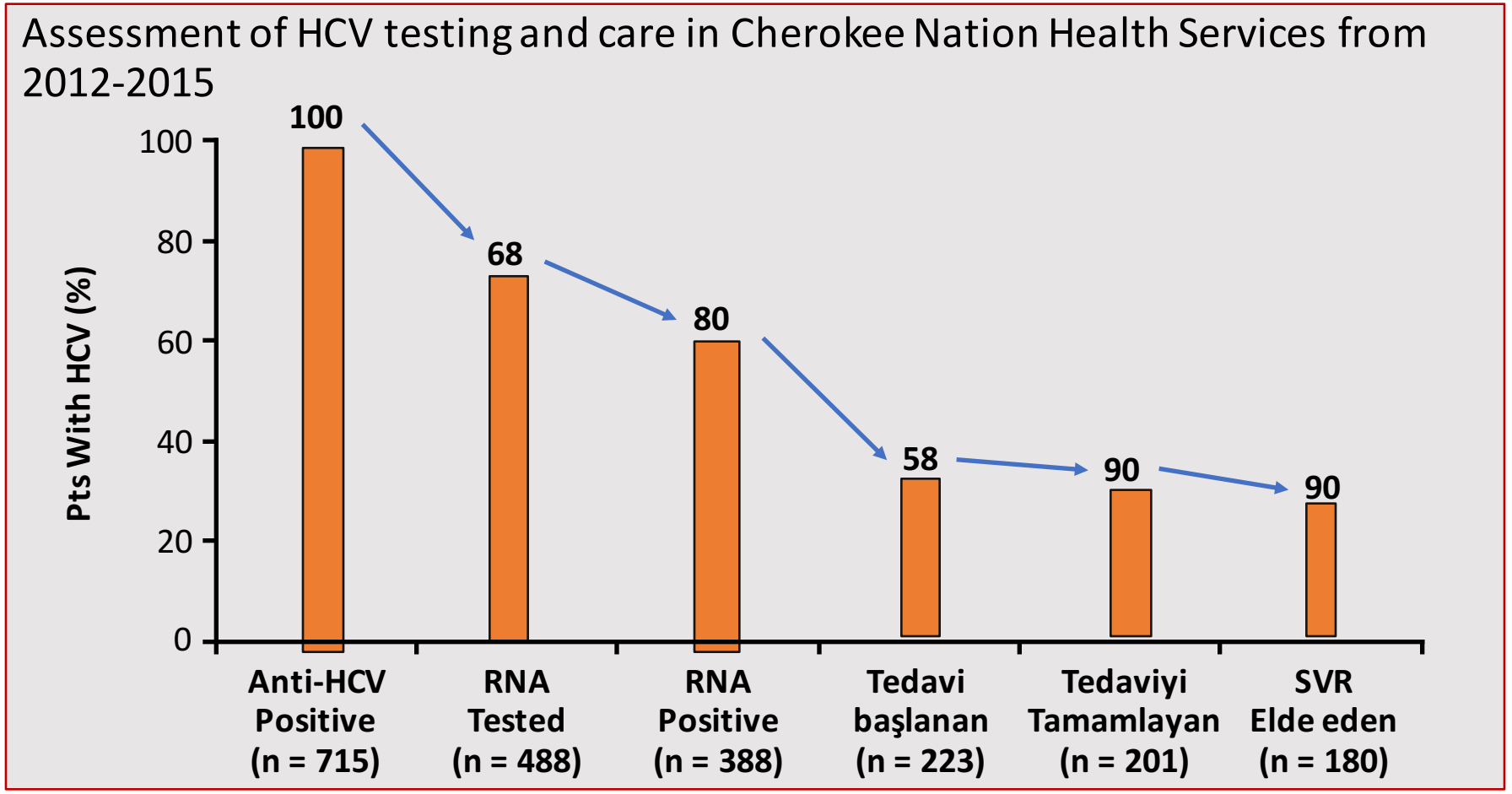
Kalıcı viral yanıtta artış



Wendy Carter. *The Journal of Clinical Pharmacology / Vol 00 No 00 2016*

Günümüzdeki sorunlar ?

ABD'de HCV : Günlük pratikteki boşluklar



Mera J, et al. *MMWR Morb Mortal Wkly Rep. 2016;65:461-466.*

PHARMACOECONOMICS

Croat Med J. 2016;57:582-90
https://doi.org/10.3325/cmj.2016.57.582

CMJ

Incremental cost-effectiveness pharmacoeconomic assessment of hepatitis C virus therapy: an approach for less wealthy members of the common market

Diana Mance[1], Davor Mance[2], Dinko Vitezić[3,4]

[1]Department of Physics, University of Rijeka, Rijeka, Croatia
[2]Faculty of Economics, University of Rijeka, Rijeka, Croatia
[3]School of Medicine, University of Rijeka, Rijeka, Croatia
[4]University Hospital Centre Rijeka, Rijeka, Croatia

Yeni kombinasyonlar özellikle deneyimli sirotik GT1 hastalarında maliyet etkindir

TABLE 2. Direct therapy costs and average therapy costs per SVR (obtained by Monte Carlo simulation) for different HCV GT1 patient subgroups and treatment regimens*

HCV GT1 patient subgroup	OBV/PTV/r/DSV		pegIFN		BOC+pegIFN		TPV+pegIFN		SIM+pegIFN	
	no cirrhosis	cirrhosis	no cirrhosis	cirrhosis	no cirrhosis	cirrhosis	no cirrhosis	cirrhosis	no cirrhosis	cirrhosis
Therapy costs (VAT included) (€)										
naive	45 000	1a: 90 000 1b: 45 000	4200/8400	8400	23 200/32 700	41 900	30 200/34 300	34 300	32 800	32 800
partial responders	45 000	1a: 90 000 1b: 45 000	8400	8400	32 700	41 900	30 200/34 300	34 300	36 900	36 900
null responders	45 000	1a: 90 000 1b: 45 000	8400	8400	41 900	41 900	34 300	34 300	36 900	36 900
Average therapy costs per successfully treated patient (€)										
naive	1a: 46 900 1b: 45 000	1a: 95 200 1b:45,000	15 000	23 700	47 300	78 300	43 600	52 400	43 200	56 000
relapsers	1a: 47 900 1b: 45 000	1a: 90 000 1b: 45 000	-	-	39 200	96 900	37 700	43 500	47 600	55 700
partial responders	45 000	1a: 90 000 1b: 52 500	-	-	55 300	116 000	49 200	93 000	54 700	59 300
null responders	1a: 47 200 1b: 45 000	1a: 96 900 1b: 45 000	-	-	108 800	-	9 900	207 400	77 400	97 100

*SVR – sustained virological response; HCV GT1 – hepatitis C virus genotype 1; 1a, 1b – HCV GT1 subtypes; OBV/PTV/r/DSV – ombitasvir, paritaprevir, ritonavir and dasabuvir; pegIFN – pegylated interferon; BOC – boceprevir; TPV – telaprevir; SIM – simeprevir

Ortalama KVY maliyeti *155,662* $

F0-2 → *122,452* $ **F3-4** → *178,401* $

Real-World Drug Costs of Treating Hepatitis C Genotypes 1-4 with Direct-Acting Antivirals: Initiating Treatment at Fibrosis 0-2 and 3-4

TABLE 3 Drug Cost Analysis

Drugs	Number of Patients Treated	Mean Drug Cost per Patient ± SD (Median)	Total Mean Drug Cost per SVR (Total Drug Cost/ Number of SVRs Achieved)	Number of Patients Treated with Fibrosis Score 0, 1, 2	Mean Drug Cost per SVR (Total Drug Cost/Number of SVRs Achieved) for Fibrosis Score 0, 1, 2	Number of Patients Treated with Fibrosis Score 3, 4	Mean Drug Cost per SVR (Total Drug Cost/Number of SVRs Achieved) for Fibrosis Score 3, 4
LED/SOF	165	119,815 ± 43,706 (113,400)	123,559 (19,769,400/160)	65	100,997 (6,463,800/64)	100	138,600 (13,305,600/96)
SOF + RBV	39	141,106 ± 49,130 (104,160)	153,347 (5,520,480/36)	19	137,053 (2,604,000/19)	20	171,558 (2,916,480/17)
LED/SOF + RBV	20	134,274 ± 42,775 (116,760)	157,969 (2,685,480/17)	3	137,200 (350,280/3)	17	220,500 (2,335,200/14)
SOF + IFN + RBV	19	136,168 ± 44,057 (117,600)	184,800 (2,587,200/14)	7	116,760 (823,200/6)	12	166,800 (1,764,000/8)
SOF + SIM	38	185,353 ± 29,297 (180,600)	251,550 (7,043,400/28)	8	180,600 (1,444,800/8)	30	279,930 (5,598,600/20)
BOC I+ IFN + RBV	8	62,160 ± 21,533 (57,960)	248,640 (497,280/2)	3	N/A[a] (140,280/0)	5	178,500 (357,000/2)
TEL + IFN + RBV	29	120,352 ± 19,836 (113,400)	373,333 (3,360,000/9)	9	188,160 (1,071,000/5)	20	604,800 (2,419,200/4)
Total[b]	322	130,391 ± 46,787 (113,400)	155,662 (41,873,160/269)	116	122,452 (13,102,320/107)	206	178,401 (28,901,040)
Total excluding TEL and BOC regimens[b]	**285**	**133,328 ± 45,930 (113,400)**	**147,348 (38,015,880/258)**	**104**	**116,379 (11,891,040/102)**	**181**	**167,467 (26,124,840/156)**
Total excluding all 24-week regimens[b]	281	116,540 ± 30,266 (113,400)	140,985 (32,426,520/230)	109	116,256 (11,625,600/100)	172	161,009 (20,931,120/130)
Total excluding all 24-week regimens and TEL and BOC regimens[b]	244	117,870 ± 46,787 (113,400)	130,453 (28,569,240/219)	97	109,624 (10,414,320/95)	147	146,411 (18,154,920/124)

Note: All costs are in U.S. dollars and are calculated using average wholesale price. Cost analyses only include cost of HCV medications, not adjunctive medications, hospital costs, or projected medical costs.

[a] *No patients achieved SVR with BOC + IFN + RBV with fibrosis score 0-2, so a mean drug cost per SVR could not be calculated.*

[b] *3D and 3D + RBV are included in the totals, but only 2 patients were treated with each regimen (4 total), so an individual cost analysis for these regimens was not completed.*

3D = ombitasvir/paritaprevir/ritonavir/dasabuvir; BOC = boceprevir; HCV = hepatitis C virus; IFN = interferon; LED = ledipasvir; N/A = not available; RBV = ribavirin; SIM = simeprevir; SOF = sofosbuvir; SVR = sustained virologic response; SD = standard deviation; TEL = telaprevir.

Timothy A. Bach. *J Manag Care Spec Pharm. 2016;22(12):1437-45*

Table 1. Primary (PS), Secondary (SS) suspect drugs in liver cases

Drug name	Brand	PS	SS	Total	Percent*
Daclatasvir	Daklinza	74	25	99	18.9%
Elbasvir-Grazoprevir	Zepatier	1	0	1	0.2%
Ledipasvir-Sofosbuvir	Harvoni	116	5	121	23.1%
Paritaprevir combinations	Viekira Pak**	120	61	181	34.5%
Simeprevir	Olysio	16	21	37	7.1%
Sofosbuvir	Sovaldi	91	80	171	32.6%

*Percent of unique cases n = 524. **Includes Technivie, Viekira XR

24 olguda HBV reaktivasyonu → 3 akut kc yetmezliği

Son yıl içinde DAA alan 524 olguda akut kc yetmezliği, 1058 olguda ciddi kc hasarı

HBV koinfektelerde dikkatli olunmalı

DAA'lar akut kc yetmezliği riskini artırıyor mu ???

HCV tedavisinde beklentiler:

Şimdiye kadar

- ✓Başarı oranı yükseldi
- ✓Süre kısaldı
- ✓Günlük doz azaldı
- ✓Yan etki azaldı
- ✓Daha fazla hasta kullanabildi

Daha ne olabilir?

- Daha da çok hastaya ulaşılabilsin
- Ucuzlasın
- Tedavi süresi kısalsın
- Yan etki azalsın (*ribavirin*)
- Pan genotip (*gt3*) etkili olsun
- İlaç etkileşimi az olsun
- Direnç bariyeri yüksek olsun
- Komplike olgularda (*böbrek, kc, nakil*) kullanılabilsin
- Yanıtsızlarda da kullanılabilsin
- Kolay yutulsun
- Temas öncesi/sonrası korusun
- Hiç ilaç almayalım !

Table 1: Direct-acting antivirals (DDAs) approved for HCV treatment or investigated in clinical trials (updated in September 2016).

Class	Generation	Approved substances (developing company)	Substances currently tested in clinical trials (developing company) [phase of development]
NS3/4A protease inhibitors	First generation	Telaprevir (Janssen, Mitsubishi) Boceprevir (Merck) Simeprevir (Janssen) Paritaprevir (AbbVie) Asunaprevir (Bristol-Myers Squibb) Vaniprevir (Merck)	
	Second generation	Grazoprevir (Merck)	ABT-493 (AbbVie) (glecaprevir) GS-9857 (Gilead Scier (voxiloprevir)
NS5A inhibitors	First generation	Daclatasvir (Bristol-Myers Squibb) Ledipasvir (Gilead Sciences) Ombitasvir (AbbVie) Elbasvir (Merck) Velpatasvir (Gilead Sciences)	Odalasvir (Janssen) [Phase 2] Ravidasvir (Presidio) [Phase 2/3]
	Second generation		ABT-530 (AbbVie) (Pibrentasvir) MK-8408 (Merck) (ruzasvir)
Nucleotide analogue inhibitors of NS5B RNA-dependent RNA polymerase	First generation	Sofosbuvir (Gilead Sciences)	MK-3682 (Merck) [Phase 2] AL-335 (Janssen) [Phase 2]
Nonnucleoside inhibitors of NS5B RNA-dependent RNA polymerase	Palm-1 inhibitors	Dasabuvir (AbbVie)	

Cecilia Trucchi, *Journal of Immunology Research 2016, Article ID 1412840*
http://dx.doi.org/10.1155/2016/1412840

Yakın gelecekte ilaç kombinasyonları

- Üçlü kombinasyonlar
- Dörtlü kombinasyonlar
- Peg/RBV ile dörtlü kombinasyonlar

Astrid Wendt.Clinical Pharmacology: Advances and Applications 2014:6 1–17

HCV New Drugs

Tuesday, January 24, 2017

What's Hot in Gastroenterology - New Drug Classes Seek to Further Improve Already Favorable Outcomes in Hepatitis C

New Drug Classes Seek to Further Improve Already Favorable Outcomes in Hepatitis C
William F. Balistreri, MD
January 24, 2017
Editor's Note: *Several major themes related to hepatitis C virus (HCV) emerged at The Liver Meeting®, the annual meeting of the American Association for the Study of Liver Diseases, held November 11-15, 2016, in Boston, Massachusetts. With the success of direct-acting antiviral (DAA) regimens, presentations focused on new drugs and ways to integrate existing and upcoming agents into treatment strategies. In addition, new data on the management of patients with HCV infection during the peri-transplant period, as well as the impact of DAAs on recurrent infection after transplantation, were presented. Of special importance was a discussion on the potential reactivation of hepatitis B virus (HBV) infection during the DAA treatment of HCV infection.*

Article available at Medscape, **free registration required.**

Index

Glecaprevir/Pibrentasvir

- GLE *(ABT-493)* / PIB *(ABT-530)*
- Pan genotipik
- Direnç bariyeri yüksek
- NS3A ve NS5A RAV lara etkili
- Günde tek doz (300 mg/120 mg).
- Böbrek hastalarında da kullanılabilir.

Sofosbuvir/Velpatasvir/Voxilaprevir

- Pan genotipik
- SOF/VEL(400 mg/100 mg) + VOX (100 mg)
- Tek tablet
- NS5A inhibitör tedavisine yanıtsızlarda etkili

Grazoprevir/Elbasvir/Ruzasvir/MK3682

- ± Ribavirin
- Tek doz
- Proteaz inh. ve NS5A RAV'lara da etkili

RG-101

- **MİR-122** karaciğere özgül mikroRNA; kolesterol ve yağ asidi sentezinde görevli,
- HCV genomuna bağlanarak **virüsü hücresel enzimlerden koruyor**,
- **RG-101, miR-122'yle etkileşiyor** → HCV replikasyonu bozuluyor (*DAA'ların etkili olduğu basamaktan çok önce*),
- DAA'lar ile **kombine** edildiğinde başarı artıyor.

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

PTC725, an NS4B-Targeting Compound, Inhibits a Hepatitis C Virus Genotype 3 Replicon, as Predicted by Genome Sequence Analysis and Determined Experimentally

Jason D. Graci,[a] Stephen P. Jung,[a] John Pichardo,[a] Frederick Lahser,[b] Xiao Tong,[c] Zhengxian Gu,[a*] Joseph M. Colacino[a]

Mevcut tedavilere yanıtsız GT1 ve GT3 olgularda kombinasyon tedavisine eklenebilir

Cell Stress and Chaperones (2017) 22:113–122
DOI 10.1007/s12192-016-0747-8

ORIGINAL PAPER

Inhibition of hepatitis C virus using siRNA targeted to the virus and Hsp90

Ana Claudia Silva Braga[1] · Bruno Moreira Carneiro[1,2] · Mariana Nogueira Batista[1] · Mônica Mayumi Akinaga[1] · Paula Rahal[1]

Isı şok proteinleri [*Heat shock protein 90 (Hsp90*)]

hücresel ve viral proteinlerin katlanmasında rol oynar

Hsp90 genine etki ederek **Hsp90'ın yok edilmesi HCV replikasyonunu da durdurmakta**

DRUG DEVELOPMENT RESEARCH 00 : 00–00 (2016)

Research Review

Epigenetic Treatment of Persistent Viral Infections

Walter H. Moos,[1]* Carl A. Pinkert,[2] Michael H. Irwin,[3] Douglas V. Faller,[4,5] Krishna Kodukula,[6] Ioannis P. Glavas,[7] and Kosta Steliou[5,8]*

SCIENTIFIC REPORTS

OPEN

Received: 05 May 2016
Accepted: 02 August 2016
Published: 31 August 2016

TRIM14 inhibits hepatitis C virus infection by SPRY domain-dependent targeted degradation of the viral NS5A protein

Shanshan Wang[1,2], Yongzhi Chen[3,4], Chunfeng Li[2], Yaoxing Wu[1], Lei Guo[1], Changwei Peng[1], Yueping Huang[1], Genhong Cheng[2,3,5] & F. Xiao-Feng Qin[1,2]

Tripartite motif 14 (TRIM14) doğal immün yanıtı düzenleyen mitokondriyal bir sinyal

Uyarıldığında hepatosit içindeki HCV replikasyonu ve enfeksiyonunu önlüyor

Monoklonal antikorlar

(*RBV ile kombine olabilir*)

HCV zarf glikoproteinleri E1 ve E2; hücre içine girişten sorumlu

Bu proteinlerin monoklonal antikorlarla engellenmesi enfeksiyonu durdurabilir !

Antiviral Research 139 (2017) 18–24

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

A profiling study of a newly developed HCVcc strain PR63cc's sensitivity to direct-acting antivirals

Wanyin Tao [a, 1], Tianyu Gan [a, b, 1], Jie Lu [a, 2], Jin Zhong [a, *]

İlaç duyarlılıklarını araştırmak için yeni hücre kültürleri

Drug Evaluation

Expert Opinion

Taribavirin in the treatment of hepatitis C

Paulina Deming & Sanjeev Arora†

Expert Opin. Investig. Drugs (2011) 20(10):1435-1443

Taribavirin, ribavirinin ön ilacı

Karaciğerde yoğunlaşıyor

Anemi riski azalıyor

Ancak virolojik yanıt da düşük

Biomedicine & Pharmacotherapy 83 (2016) 881–891

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Therapeutic potential of *Taraxacum officinale* against HCV NS5B polymerase: *In-vitro* and *In silico* study

Sidra Rehman[a,*], Bushra Ijaz[b], Nighat Fatima[c], Syed Aun Muhammad[d]
Sheikh Riazuddin[e]

Pakistan dergisi, impact factor: 2,326

T. officinale = Karahindiba = Radika

Sofosbuvir kontrol grubuyla karşılaştırılmış

Etkinlikleri benzer bulunmuşlar

Aşı çalışmaları

TABLE 6: Preventive hepatitis C virus vaccine tested in clinical trials.

Type of vaccine	Viral component	Adjuvant	Phase of clinical trial	Study population
Recombinant protein	Recombinant E1 protein	Aluminum hydroxide	I	20 healthy subjects
	Recombinant E1 and E2 proteins	MF59	I	60 healthy subjects
	Recombinant core protein	ISCOMATRIX	I	60 healthy subjects
Peptide	Five synthetic peptides derived from conserved regions of core, NS3, and NS4 proteins of HCV genotypes 1 and 2 (IC41)	Poly-L-arginine	I	128 healthy subjects
	Five synthetic peptides derived from conserved regions of core, NS3, and NS4 proteins of HCV genotypes 1 and 2 (IC41)	Poly-L-arginine	I	54 healthy subjects
Virally vectored	Human adenovirus rare serotype 6 (HADV6) and chimpanzee Ad 3 (ChAd3) expressing the HCV nonstructural proteins	–	I	30 healthy subjects

Trucchi C. J Immunol Res 2016

Aşı önündeki engeller

- Sık mutasyon (*quasispecies*)
- Doğal bağışıklıktan kaçış (*antikor ve hücresel*)
- Kazanılmış bağışıklıkta zayıf ve etkisiz yanıt
- Uygun deneysel bir modelin olmayışı (*yalnız şempanzeler !*)

WHO GLOBAL HEALTH SECTOR STRATEGY ON VIRAL HEPATITIS, 2016–2021

TARGET AREA	BASELINE 2015	2020 TARGETS	2030 TARGETS
Impact targets			
Incidence: New cases of chronic viral hepatitis B and C infections	Between 6 and 10 million infections are reduced to 0.9 million infections by 2030 (95% decline in hepatitis B virus infections, 80% decline in hepatitis C virus infections)	30% reduction (equivalent to 1% prevalence of HBsAg[9] among children)	90% reduction (equivalent to 0.1% prevalence of HBsAg among children)[10]
Mortality: Viral hepatitis B and C deaths	1.4 million deaths reduced to less than 500 000 by 2030 (65% for both viral hepatitis B and C)	10% reduction	65% reduction
Viral hepatitis B and C diagnosis	<5% of chronic hepatitis infections diagnosed	30%	90%
Viral hepatitis B and C treatment	<1% receiving treatment	5 million people will be receiving hepatitis B virus treatment 3 million people have received hepatitis C virus treatment (Both targets are cumulative by 2020)	80% of eligible persons with chronic hepatitis B virus infection treated 80% of eligible persons with chronic hepatitis C virus infection treated

2030'da hedefi tutturabilmek için en az 70 milyon kişiye ulaşabilmeli,

İlaçlar çok pahalı,

Jenerikler kontrol altına alınmazsa dirençli suşlar artabilir,

Aşı olmadan mümkün değil.

Hepatitis C Drugs: Is Next Generation the Last Generation?

JEAN-MICHEL PAWLOTSKY
http://dx.doi.org/10.1053/j.gastro.2016.08.043

- ✓ **Sonraki jenerasyon son olacak,**
- ✓ **Bundan sonraki ilaçlarda minör değişiklikler olabilir;**
  - ✓ **İlaç endüstrisi diğer alanlara kaymakta**
- ✓ **Ancak hala milyonlar HCV'den habersiz;**
- ✓ **HCV'nin eradike olabilmesi için tarama, tanı ve korunma üzerine plan yapılmalı**

Yakın Gelecek Şeması

Tedavi süresi : 4-8 hafta

Perfectoprebutasvir
Günde 1 tablet

Etkinlik : >%95

Transplantation Publish Ahead of Print
DOI: 10.1097/TP.0000000000001596

Successful Continuation of HCV Treatment Following Liver Transplantation

Carlos Fernández Carrillo, MD[1], Gonzalo Crespo, MD, PhD[2], Juan de la Revilla, MD[1], Lluís

- ✓ Nakil öncesi tedavinin bitirilmiş olması önerilmekte

- ✓ Ancak elde olmayan nedenlerle tedaviye ara verilmesi (2-33 gün) ve nakil sonrası sürdürülmesi yanıtı düşürmüyor.

Potadaki DAA

AASLD Boston 2016

İlaç	Kısaltma	Sınıf
Glecaprevir (formerly ABT-493)	GLE	NS3/4A protease inhibitor
Voxilaprevir	VOX	NS3/4A protease inhibitor
Pibrentasvir (formerly ABT-530)	PIB	NS5A inhibitor
Ruzasvir (formerly MK-8408)	RZR	NS5A inhibitor
MK-3682	--	NS5B polymerase nucleotide inhibitor

Slide credit: clinicaloptions.com

HBV Reactivation Associated With DAA Therapy

- A recent surveillance of the US Food and Drug Administration (FDA) database suggested that there is an increased risk for reactivation in patients with past HBV infection who are initiating DAA therapy for HCV infection. The FDA issued a black- box warning in October 2016 regarding this newly established risk for HBV reactivation. Revised HCV DAA labeling indicates that all patients should be screened for evidence of current or previous HBV infection before the initiation of DAA therapy. Patients with previous HBV infection should be monitored for signs of possible HBV reactivation.

Önemli direnç varyantları(RAV resistant associated variants)

R155K	A replicatively fit variant in the HCV protease that confers resistance to 1st-generation protease inhibitors
Q80K	A variant present at baseline in many GT1a HCV patients that reduces efficacy of simeprevir combined with PEG-IFN+RBV
Y93H	One of several RAVs in the NS5A protein; Y93H has a many-fold effect on EC50

Sorunlar devam etmekte

GT3 sirozlular
Dekompanze sirozlular
GT2 ve GT3 böbrek yetmezlikliler

However, areas for improvement still remain,in particular for those with HCV GT 3 with cirrhosis,those with decompensated cirrhosis, and those withsevere renal disease who are infected with HCV GT 2or GT 3. Additionally, effective treatment options withhigh barriers to resistance are needed for retreatmentof patients who have failed a prior HCVDAA regimen.With the rapid availability of newHCVDAAtreatmentregimens and the multiple factors to consider whenstarting an individual patient on appropriate HCVtherapy, the complexity of treatment selection has alsoincreased. Future HCV regimens on the horizon may further address the treatment needs of some difficul tto-treat subgroups and special populations and potentially streamline treatment recommendations.A further major obstacle for the control of thedisease is represented by the lack of availability of an effectivescreening strategy to identify all people in need of treatment.

- Viral Immunol. 2017 Jan 23. doi: 10.1089/vim.2016.0111. [Epub ahead of print]
- **Oral Combination Vaccine, Comprising Bifidobacterium Displaying Hepatitis C Virus Nonstructural Protein 3 and Interferon-α, Induces Strong Cellular Immunity Specific to Nonstructural Protein 3 in Mice.**
- Kitagawa K[1], Omoto C[2], Oda T[2], Araki A[2], Saito H[1], Shigemura K[2,3], Katayama T[4], Hotta H[2], Shirakawa T[1,2,3,5].
- **Author information**
- **Abstract**
- We previously generated an oral hepatitis C virus (HCV) vaccine using Bifidobacterium displaying the HCV nonstructural protein 3 (NS3) polypeptide. NS3-specific cellular immunity is important for viral clearance and recovery from HCV infection. In this study, we enhanced the cellular immune responses induced by our oral HCV vaccine, Bifidobacterium longum 2165 (B. longum 2165), by combining interferon-α (IFN-α) as an adjuvant with the vaccine in a mouse experimental model. IFN-α is a widely used cytokine meeting the standard of care (SOC) for HCV infection and plays various immunoregulatory roles. We treated C57BL/6N mice with B. longum 2165 every other day and/or IFN-α twice a week for a month and then analyzed the immune responses using spleen cells. We determined the induction of NS3-specific cellular immunity by cytokine quantification, intracellular cytokine staining, and a cytotoxic T lymphocyte (CTL) assay targeting EL4 tumor cells expressing NS3/4A protein (EL4-NS3/4A). We also treated mice bearing EL4-NS3/4A tumor with the combination therapy in vivo. The results confirmed that the combination therapy of B. longum 2165 and IFN-α induced significantly higher IFN-γ secretion, higher population of $CD4^+$T and $CD8^+$T cells secreting IFN-γ, and higher CTL activity against EL4-NS3/4A cells compared with the control groups of phosphate-buffered saline, B. longum 2165 alone, and IFN-α alone ($p < 0.05$). We also confirmed that the combination therapy strongly enhanced tumor growth inhibitory effects in vivo with no serious adverse effects ($p < 0.05$). These results suggest that the combination of B. longum 2165 and IFN-α could induce a strong cellular immunity specific to NS3 protein as a combination therapy augmenting the current SOC immunotherapy against chronic HCV infection.

Table 5 Estimate of first approval for the new HCV treatments in the USA and Europe

Protease inhibitor	Company	Current clinical phase	FDA approval expected	EMEA approval expected
Simeprevir TMC-435[14,15]	Tibotec	III	2013	2014
Faldaprevir BI-201 135[16,17]	Boehringer Ingelheim	III	2014	2014
Danoprevir (ITMN-191, RG 7227)[18,19]	Roche	II	2015?	2015 ?
Vaniprevir (MK-7009)[20,21]	Merck	III	No 2014(Japon)	No
ABT-450[22]	Abbott	III	2014	2014
Sovaprevir ACH-1625[23]	Achillion	II	?	?
Asunaprevir BMS-650032[24,25]	BMS	III	2014	2014
GS-9256[67]	Gilead	II	?	?
MK-5172	MSD	II	2015/2016	2015/2016
Polymerase inhibitors				
RG-7128 Mericitabine [31–33]	Roche	II	?	?
GS- 7977 Sofosbuvir[34–38]	Gilead	III	2013	2013
NNI-Site I inhibitors BI 207 127[39]	Bohringer Ingelheim	III	2014	2014
NNI-Site I inhibitors BMS 791325[73]	BMS	II	2014/2015	2014/2015
NNI-Site 2 inhibitors Filibuvir[40]	Pfizer	II	?	?
NNI-Site 2 inhibitors VX-222[41]	Vertex	II	?	?
NNI-Site 3 inhibitors Setrobuvir ANA598[42]	Anadys	I	?	?
NNI-Site 3 inhibitors ABT-333[43]	Abbott	III	2014	2014
NNI-Site 3 inhibitors ABT-072[43]	Abbott	II	?	?
NNI-Site 4 inhibitors Tegobuvir (GS9190)[44]	Gilead	II	?	?
NS5A-inhibitor				
Daclatasvir (DCV) BMS-790052[46–48]	BMS	III	2014	2014
ABT 267[51]	Abbott	III	2014	2014
Ledipasvir GS-5885	Gilead	III	2014	2014

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