KRONIK HEPATIT C OLGU SUNUMU

Dr. Elif SARGIN ALTUNOK

58 Yaşında Kadın Hasta

- 2006 yılında anti HCV pozitif

- Özgeçmişinde; 15 yıl önce kolesistektomi
  Hipertansiyon ve Tip 2 diabetes mellitus
  CO-İRDA (İrbesartan+Hidroklorotiyazid)

- Fizik muayenesinde; 1.60 boyunda, 85 kg ağırlığında
  Sistem muayenelerinde özellik yok

Laboratuvar Bulguları

AST, U/L	59	HBsAg	Negatif
ALT, U/L	56	Anti HBs	Negatif
Total Protein, g/dL	7.98	Anti HIV	Negatif
Albumin, g/dL	4.26	**Anti HCV**	**Pozitif**
Total Bilirubin, mg/dL	0.4	**HCV RNA kopya/mL**	**1.040.000**
Direk Bilirubin, mg/dL	0.2	**GENOTİP**	**1a/1b**
Trombosit, 10^3/mm3	285000	**IL 28B rs12979860 C/T polimorfizmi**	**CT**
INR	1.05	Batın Ultrasonografisi	Özellik yok

HCV RNA Pozitif Devam Eden Hastaya Karaciğer Biyopsisi Yapıldı;

Tanı

- **Kronik C hepatiti**
- **Grade-Aktivite İndeksi: 3**
- **Stage-Fibrozis İndeksi: 1**

Prof.Dr.Yeşim Gürbüz

Kocaeli Üniversitesi Tıp Fakültesi Patoloji AD

BIRINCI TEDAVI (2006)

- Pegile interferon alfa 2a 180 mg/hafta ve ribavirin 1200 mg/gün
- Tedavinin 3.ayında HCV RNA negatif
- 48 haftaya tedaviyi sorunsuz olarak tamamladı
- Tedavi sonu HCV RNA negatif

- Tedavi bittikten sonraki 3.ay kontrolünde HCV RNA tekrar pozitif
- **RELAPS**

IL 28B Genotipi

- Hepatit C virus enfeksiyonunda tedaviye cevabı öngören faktörler arasında IL 28B polimorfizminin önemli bir belirleyici olduğu yapılan çalışmalarda gösterildi.
- HCV genotip 1 ve 4 için tedavi sonucunu öngörebiliyor
- Genotip 2 ve 3 daha fazla interferon duyarlı oldukları için IL28B sonuçları cevapla daha az ilişkili bulunmuş

Elmer Press

Original Article

Gastroenterol Res. 2014;7(5-6):123-130

Impact of Interleukin 28B Genotype on the Virological Responses in Chronic Hepatitis C Treatment

Bilgehan Aygen[a], Orhan Yildiz[a, h], Sila Akhan[b], Ozgur Gunal[c], Serpil Taheri[d], Gokmen Zararsiz[e], Murat Sayan[f], Aydin Rustemoglu[g], Elif Sargin Altinok[f]

Table 4. Relationship Between IL28B Genotype and Response to Treatment Rates

Variables, n (%)	C/C (n = 42)	C/T (n = 98)	T/T (n = 46)	P
RVR	23 (54.8)	39 (41.9)[a]	18 (39.1)	0.216
cEVR	37 (88.1)	57 (58.2)	22 (47.8)	< 0.001
EVR (cEVR + pEVR)	41 (97.6)	71 (72.4)	29 (63.0)	< 0.001
ETR	38 (90.5)	61 (62.2)	26 (56.5)	0.001
SVR	28 (66.7)	42 (42.9)	13 (28.3)	0.001
Relapse	11 (26.2)	20 (20.4)	14 (30.4)	0.400
PR	1 (2.4)	8 (8.2)	3 (6.5)	0.443
NR	1 (2.4)	25 (25.5)	16 (34.8)	0.001
Breakthrough	1 (2.4)	3 (3.1)	0 (0.0)	0.495

RVR: rapid virological response; cEVR: complete early virological response; EVR: early virological response; pEVR: partial early virological response; ETR: end-of-treatment response; SVR: sustained virological response; PR: partial response; NR: null response. [a]Five patients were not evaluated for RVR.

İKINCI TEDAVI (2009)

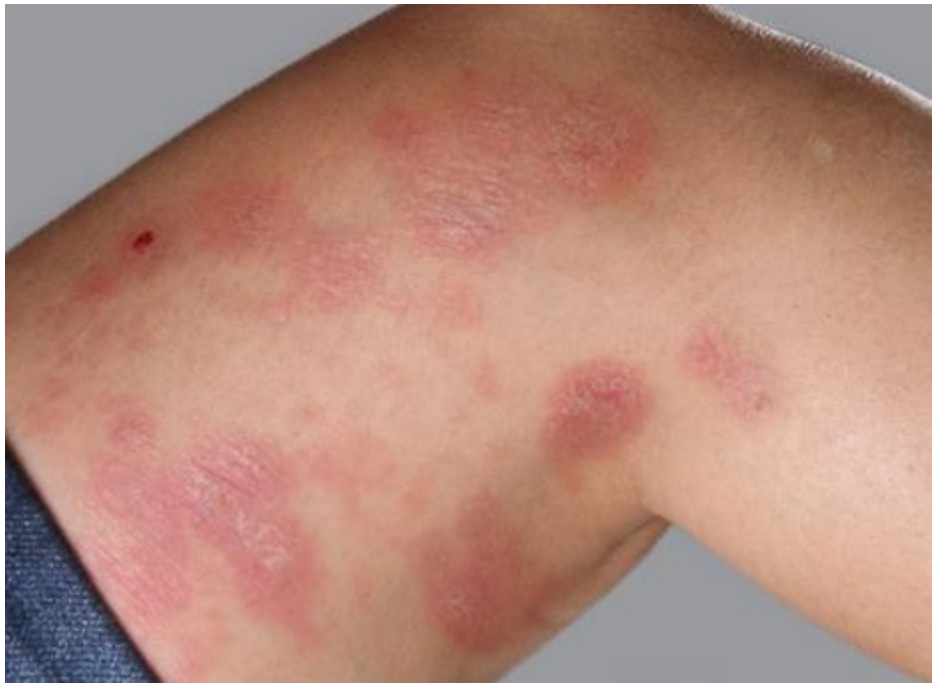
AST, U/L	54	Total Protein, g/dL	8
ALT, U/L	51	Albumin, g/dL	4.3
Trombosit, 10^3/mm3	319000	AFP, ng/ml	6.8
HCV RNA IU/mL	**3.960.000**		

- Pegile interferon alfa 2b 150 mg ve ribavirin 1200 mg ile başlandı
- Tedavini 1.ayı; HCV RNA: 1,490,000

  Yüzünde ve bacaklarında döküntülü plak şeklini alan kızarıklar başladı

- **TEDAVİSİ SONLANDIRILDI**

Deri Biyopsisi Yapıldı;



- **MAKROSKOPİ: I-** Üzerinde 0,2 cm boyutta deri elipsi bulunan 0,2 cm derinliğinde doku parçası. 1/Y

II- Üzerinde 0,2 cm boyutta deri elipsi bulunan 0,3 cm derinliğinde doku parçası. 1/Y

- **TANI : I- Alın, Deri-punch Biopsi: Liken planus** ile uyumlu bulgular.

II- Bacak, Deri-punch Biopsi: Ortohiperkeratoz, epidermiste incelme, perivasküler nonspesifik kronik yangı

KHC-Ekstrahepatik Bulgular

- Hepatit C virusu **immünolojik mekanizmalarla** dolaylı veya **sitopatik etkiyle** doğrudan ekstrahepatik semptom ve bulguların patogenezinde rol oynamaktadır

- Hepatit C hastalarının %40-74'ünde HCV ilişkili ekstrahepatik bulgular görülmektedir

- Kronik HCV enfeksiyonunda oluşan ekstrahepatik sendromlar **kronik, sürekli ve kalıcıdır**

Zignego AL et al. Dig Liver Dis 2007;39(Suppl), S38–S45.

Galossi A, et al. Gastrointestin Liver Dis 2007; 16: 65-73.

KHC-Ekstrahepatik Bulgular

- Esansiyel mikst kryoglobulinemi
- Membranöz glomerulonefrit ve membranoproliferatif glomerulonefrit
- Poliarteritis nodosa
- Porfiria kutanea tarda
- Sjöngren's sendromu
- **Liken planus**
- İdiyopatik pulmoner fibrozis
- Mooren's korneal ülserasyon
- Otoimmün tiroidit
- **Tip-2 diabetes mellitus**
- Behçet Hastalığı ve çeşitli otoantikor pozitiflikleri

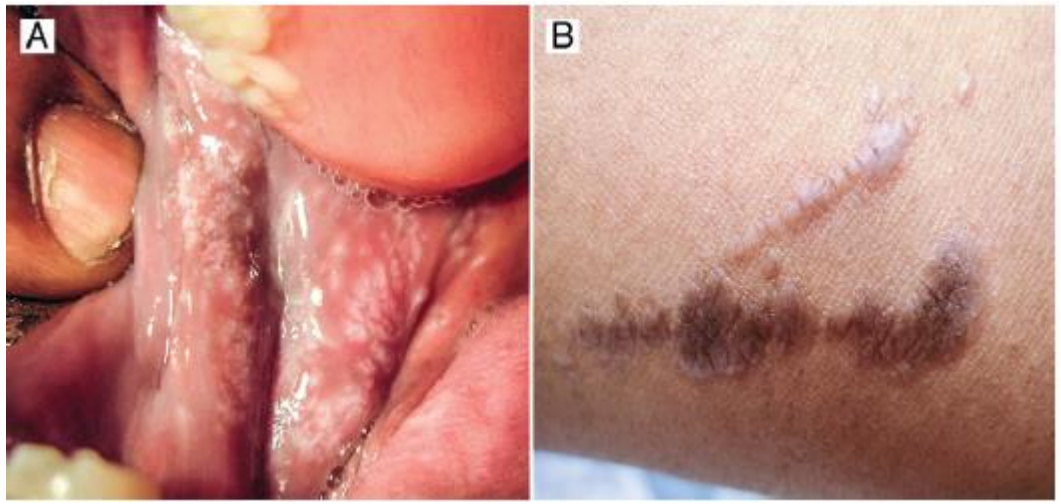
Review Article

Dermatologic Extrahepatic Manifestations of Hepatitis C

Bhavtosh Dedania* and George Y. Wu

Department of Medicine, Division of Gastroenterology-Hepatology, University of Connecticut Heath Center, Farmington, CT, USA

Journal of Clinical and Translational Hepatology **2015** vol. 3 | 127–133



- Yapılan çalışmalarda HCV infeksiyonunun tedavisi ile LP semptomlarının iyileşmesi arasında ki ilişki bugüne kadar tutarsız olarak bildirilmiş (iyileşme, alevlenme).
- Özellikle IFN dayalı HCV tedavilerinde tüm LP lezyonlarının gerilemediğini göstermektedir.
- Şuana kadar DAAs için ise veri bulunmamaktadır

Kronik Hepatit-C Virüsü Enfeksiyonunda Ekstrahepatik Bulguların Prevalansının Değerlendirilmesi

THE EVALUATION OF THE PREVALENCE OF EXTRAHEPATIC FINDINGS IN CHRONIC HEPATITIS-C VIRUS INFECTION

Dr. Ali Kemal KADİROĞLU,[a] Dr. Vedat GÖRAL,[b] Dr. Dede ŞİT,[a]
Dr. Murat ÇELİK,[c] Dr. M. Emin YILMAZ[d]

[a]İç Hastalıkları AD, [b]Gastroenteroloji BD, [d]Nefroloji BD, Dicle Üniversitesi Tıp Fakültesi, DİYARBAKIR
[c]İç Hastalıkları Kliniği, Nusaybin Devlet Hastanesi, MARDİN

Tablo 3. Grupların ekstrahepatik bulgularının karşılaştırılması.

Ekstrahepatik manifestasyonlar	Anti-HCV (+) grup n= 40	HbsAg (+) grup n= 40	p
Romatolojik Bulgular	%	%	
Artralji	25	5	p= 0.031
Artrit	5	0	
Nörolojik Bulgular			
Parestezi	10	5	p= 0.041
Periferik nöropati	12.5	0	
Psikiyatrik Bulgular			
Depresyon	50	7.5	p= 0.000
Anksiyete	2.5	0	
Otoantikor Pozitifliği			
ANA (+)	25	5	
ASMA (+)	2.5	0	p= 0.006
ANA+ASMA+AMA (+)	7.5	0	
Dermatolojik Bulgular			
Pruritus	10	2.5	
Liken planus	5	0	p= 0. 045

Turkiye Klinikleri J Med Sci 2005, 25:621-626

Eur J Epidemiol. 2000;16(12):1159-61.

The prevalence of hepatitis C virus infection in patients with lichen planus in Gaziantep region of Turkey.

Kirtak N[1], Inalöz HS, Ozgöztasi, Erbağci Z.

Author information

Abstract

The purpose of this case-control study was to investigate the association between lichen planus (LP) and hepatitis C virus (HCV) infection in Gaziantep region of Turkey. Seventy-three patients with LP and a control group of patients (n: 73) with a dermatological disorder other than LP were detected for HCV infection using a third generation enzyme-linked immunosorbent assay (ELISA). A serological positivity for HCV was found in five of LP patients (6.84%), whereas it was positive for only one patient of the control group (1.36%). A statistically significant difference was found between LP and control groups ($p < 0.05$). We conclude that the coexistence of the two diseases is probably more than coincidental.

- Türkiye ve Tayland'da yapılan bazı çalışmalarda ise LP ve HCV arasındaki ilişki gösterilememiş (rastlantısal ?).

İkinci Kez Karaciğer Biyopsisi Yapıldı (06.09.2012)

Tanı

- **Kronik C hepatiti**
- **Grade-Aktivite İndeksi: 10**
- **Stage-Fibrozis İndeksi: 4**

Prof.Dr.Yeşim Gürbüz

Kocaeli Üniversitesi Tıp Fakültesi Patoloji AD

ÜÇÜNCÜ TEDAVI (2014)

Daklatasvir + Asunaprevir

- Daklinza 1x 60 mg /gün
- Sunvepra 2x 100 mg /gün

Takiplerinde yan etki görülmedi

Tedavisi 24 haftaya tamamlandı

SVR

	Başlangıç	1.ay	3.ay	6.ay	TS 3.ay
HCV RNA, IU/mL	**580000**	**Negatif**	**Negatif**	**Negatif**	**Negatif**
AST, U/L	44	22	20	19	22
ALT, U/L	41	16	16	13	17
Total Protein, g/dL	6.7	7.5	7.4	7.9	7.2
Albumin, g/dL	3.4	3.8	4	4.2	4.3
Total Bilirubin, mg/dL	0.6	0.5	0.6	0.4	0.6
Direk Bilirubin, mg/dL	0.3	0.2	0.2	0.2	0.2
Trombosit, 10^3/mm3	204	246	218	250	234
INR	1	1.1	1	1	0.9
AFP mIU/L	11.5	11.6	7	8.4	9.9

Drugs. 2014 Sep;74(13):1559-71. doi: 10.1007/s40265-014-0279-4.

Daclatasvir + asunaprevir: first global approval.

Poole RM[1].

Author information

Abstract

The combination of daclatasvir + asunaprevir [Daklinza(®) + Sunvepra(®) (Japan)], two direct-acting antiviral agents, has been developed by Bristol-Myers Squibb for the treatment of patients with chronic hepatitis C virus (HCV) genotype 1 infections, including those with compensated cirrhosis. Daclatasvir + asunaprevir has received its first global approval in this indication in Japan. Daclatasvir + asunaprevir is the first all-oral, interferon- and ribavirin-free regimen for this indication. This article summarizes the milestones in the development of daclatasvir + asunaprevir leading to this first approval for the treatment of chronic HCV genotype 1 infections.

PMID: 25117197 [PubMed - indexed for MEDLINE]

- **Daklatasvir ve asunaprevir** kombinasyonu ilk olarak Japonya'da ve diğer HCV genotip 1b hastalarının çok olduğu Kore ve Tayvan'da onaylanmıştır.

- Avrupa'da **Daklatasvir ve sofosbuvir** kombinasyonu olarak kullanılabilmektedir.

Hepatology. 2014 Jun;59(6):2083-91. doi: 10.1002/hep.27113. Epub 2014 Apr 1.

Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection.

Kumada H[1], Suzuki Y, Ikeda K, Toyota J, Karino Y, Chayama K, Kawakami Y, Ido A, Yamamoto K, Takaguchi K, Izumi N, Koike K, Takehara T, Kawada N, Sata M, Miyagoshi H, Eley T, McPhee F, Damokosh A, Ishikawa H, Hughes E.

Author information

Abstract

All-oral combinations of direct-acting antivirals may improve efficacy and safety outcomes for patients with hepatitis C virus (HCV) infection, particularly those who are poor candidates for current interferon/ribavirin-based regimens. In this open-label, phase 3 study, 135 interferon-ineligible/intolerant and 87 nonresponder patients with chronic HCV genotype 1b infection were enrolled at 24 centers in Japan. Patients received daclatasvir 60 mg once daily plus asunaprevir 100 mg twice daily for 24 weeks. The primary endpoint was sustained virologic response 24 weeks after treatment (SVR24). This study is registered with ClinicalTrials.gov (NCT01497834). SVR24 was achieved by 87.4% of interferon-ineligible/intolerant patients and 80.5% of nonresponder (null and partial) patients; rates were similar in cirrhosis (90.9%) and noncirrhosis (84.0%) patients, and in patients with IL28B CC (84.5%) or non-CC (84.8%) genotypes. Fourteen patients in each group (12.6%) discontinued dual therapy, mainly due to adverse events or lack of efficacy. Nine nonresponder patients received additional treatment with peginterferon/ribavirin per protocol-defined criteria. The rate of serious adverse events was low (5.9%) and varied among patients. The most common adverse events were nasopharyngitis, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST), headache, diarrhea, and pyrexia.

CONCLUSION: Interferon-free, ribavirin-free all-oral therapy with daclatasvir and asunaprevir for 24 weeks is well tolerated and can achieve a high rate of SVR in patients with HCV genotype 1b who were ineligible, intolerant, or had not responded to prior interferon-based therapy. (Hepatology 2014;59:2083-2091).

- Sirotik hastalarda KVY oranı %90.9
- Non-sirotik hastalarda KVY oranı %84
- IL28B CC genotipi olanlarda KVY oranı %84.5; non-CC olanlarda %84.8

*Hastaların %12,6'sında yan etkiler nedeniyle tedavi sonlandırılmış.

(nazofarenjit, KCFT yüksekliği, baş ağrısı, ishal ve ateş)

Hepatol Res. 2015 Nov 27. doi: 10.1111/hepr.12629. [Epub ahead of print]

Improvement of renal dysfunction in a patient with HCV-related liver cirrhosis by daclatasvir and asunaprevir combination therapy: A case report.

Tsuge M[1,2,3], Hiramatsu A[1,2], Shinohara F[1,2], Nakano N[1,2], Nakamura Y[1,2], Hatooka M[1,2], Morio K[1,2], Morio R[1,2], Kan H[1,2], Fujino H[1,2], Uchida T[1,2], Kobayashi T[1,2], Fukuhara T[1,2], Masaki K[1,2], Nakahara T[1,2], Ono A[1,2], Nagaoki Y[1,2], Miki D[1,2,4], Kawaoka T[1,2], Hiraga N[1,2], Imamura M[1,2], Kawakami Y[1,2], Aikata H[1,2], Ochi H[1,2,4], Hayes CN[1,2], Chayama K[1,2,4].

⊕ Author information

Abstract

Recently, treatments for chronic hepatitis C virus (HCV) infection have been drastically improved by the development of direct-acting antiviral agents. In September 2014, dual oral therapy using daclatasvir (DCV) and asunaprevir (ASV) was approved for the treatment of chronic HCV infection in Japan. We treated a patient with HCV-related liver cirrhosis with severe leg edema due to chronic renal dysfunction using this dual oral therapy. Although serum ALT increased rapidly during the first week of treatment, the antiviral therapy was able to continue, and liver function recovered spontaneously. After one month of treatment, serum HCV RNA became continuously undetectable, and serum albumin level gradually increased. Throughout the therapy, serum creatinine level nearly normalized, and leg edema gradually improved. These improvements continued after the combination therapy was completed. HCV RNA remained undetectable following the end of therapy, and sustained virological response at 12 weeks was achieved. It has been reported that chronic HCV infection is associated with renal dysfunction and that HCV eradication can improve it. DCV and ASV combination therapy is safe for patients who have renal dysfunction and may be a suitable therapy for chronic hepatitis C patients with renal dysfunction.

- DCV ve ASV kombinasyonu ile tedavi edilen sirotik bir HCV hastasında tedavi ile kronik renal disfonksiyonun düzeldiği gösterilmiş.
- DCV ve ASV kombinasyon tedavisi böbrek fonksiyon bozukluğu olan kronik hepatit C hastaları için uygun bir tedavi olabilir.

Ther Clin Risk Manag. 2014 Jun 26;10:493-504. doi: 10.2147/TCRM.S66731. eCollection 2014.

Asunaprevir, a protease inhibitor for the treatment of hepatitis C infection.

Gentile I[1], Buonomo AR[1], Zappulo E[1], Minei G[1], Morisco F[2], Borrelli F[1], Coppola N[3], Borgia G[1].

Author information

[1]Section of Infectious Diseases, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy.
[2]Section of Gastroenterology, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy.
[3]Section of Infectious Diseases, Department of Mental Health and Public Medicine, Second University of Naples, Naples, Italy.

Abstract

According to the World Health Organization, approximately 150 million people worldwide are chronic carriers of hepatitis C virus (HCV). HCV infection can evolve into cirrhosis of the liver and its complications, which are ultimately responsible for more than 350,000 deaths every year. Antiviral therapy, when successful, is able to decrease the rate of progression and increase survival. Two types of therapies are currently available, ie, interferon-based therapies and interferon-free ones. The latter have several advantages in terms of safety and tolerability, and could be used even in the most advanced stages of the disease. However, their use is restricted to some viral genotypes (genotype 2 and 3) and they are expensive. Several molecules are in an advanced phase of development. This review deals with the pharmacokinetics, pharmacodynamics, tolerability, and safety of asunaprevir, an inhibitor of HCV nonstructural 3 protease. Asunaprevir exerts optimal in vitro activity particularly against HCV genotypes 1 and 4, and its pharmacokinetic profile enables twice daily administration. The drawback of asunaprevir, and of all protease inhibitors, is its low barrier to resistance. Consequently, it is used in association with other drugs to prevent resistance. Specifically, when combined with daclatasvir, an NS5A inhibitor, asunaprevir results in a very high rate of viral eradication in both treatment-naïve and treatment-experienced patients, with a sustained virological response rate of 80%-90%. Tolerability is fair; in fact, asunaprevir is associated with a transient increase in aminotransferase levels, which is mild in most cases. In conclusion, asunaprevir is a good candidate component of interferon-free combinations and may revolutionize the treatment of chronic HCV infection in the near future.

- Bazı hastalarda bilirubin ve aminotransferaz seviyelerinde artış görülebilmektedir
- Hepatotoksisite çoğu durumda hafif ve doza bağımlıdır
- Dekompanse sirozu olan hastalarda (Child-Pugh class B ve C) kullanımı önerilmemektedir

- Daklatasvir yapısal olmayan protein NS5A proteininin güçlü bir inhibitörüdür ve bütün genotiplere etkilidir.

- Düşük-orta genetik bariyeri nedeniyle diğer DAA ile kombine olarak kullanılmaktadır.

- Diğer DAA ile birlikte daklatasvir kombinasyon rejimlerinin kronik hepatit C tedavisinde etkinliği ve tolere edilebilirliği artırdığı görülmektedir.

Fujii Y et al. Hepatology. 2015 Jan;61(1):400-1.
Kumada H et al. J Gastroenterol Hepatol. 2015
Gastroenterol Hepatol. 2015
Int. 2015
Sundaram V et al. . Expert Rev
Everson GT, et al. Liver

TEŞEKKÜRLER