Trattamento del paziente dializzato

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Agenda

- Premesse e dimensioni del problema
- La SOC nel paziente in emodialisi
- Boceprevir e Telaprevir
- I DAAs di seconda generazione

HCV and Kidney Diseases

- HCV-associated kidney diseases
- HCV infection in patients with kidney diseases

HCV-associated kidney diseases

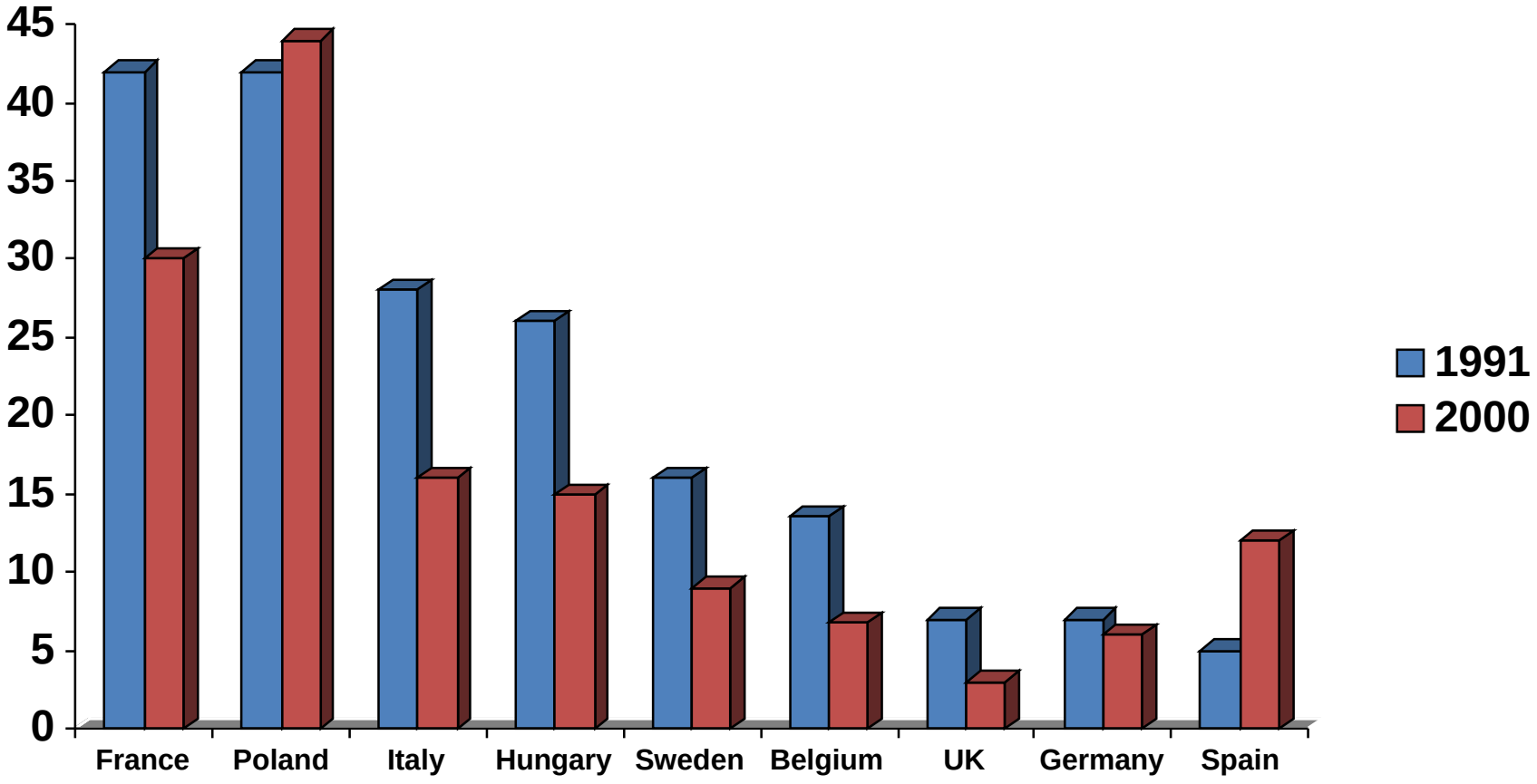
Kidney Disease	Pathogenesis	Clinical Manifestations
Cryoglobulinemic membranoproliferative glomerulonephritis	Mesangial deposits of immune complexes (HCV viral antigens, Ig, and complement fragments); cryoglobulin deposition in glomerular capillaries, mesangium, and urinary space	Nephritic syndrome, nephrotic syndrome
Noncryoglobulinemic membranoproliferative glomerulonephritis	Mesangial deposits of immune complexes (HCV viral antigens, Ig, and complement fragments)	Nephritic syndrome, nephrotic syndrome
Noncryoglobulinemic membranous glomerulopathy	Subepithelial deposits of immune complexes (HCV viral antigens, Ig, and complement fragments)	Nephrotic syndrome
Noncryoglobulinemic IgA nephropathy	Mesangial deposits of immune complexes (HCV viral antigens, Ig, and complements fragments)	Isolated proteinuria and/or hematuria
Noncryoglobulinemic focal segmental glomerulosclerosis	Direct injury by HCV on podocytes of epithelial cells	Nephrotic syndrome, isolated proteinuria
Immunotactoid glomerulopathy fibrillary glomerulonephritis	Mesangial and capillary wall deposition of immune complexes (HCV viral antigens, Ig, and complement fragments)	Nephrotic syndrome, isolated proteinuria and/or hematuria
Mesangial proliferative glomerular nephritis	Direct effect of HCV on mesangium by TLR-3 or MMP-2	Isolated proteinuria and/or hematuria
Tubulointerstitial nephritis	HCV deposition in tubular epithelial and infiltrating cells (direct cytotoxicity and/or immune-mediated injury)	Proteinuria
Thrombotic microangiopathy	Endothelial injury by direct activity of HCV	Nephrotic syndrome, isolated proteinuria and/or hematuria

Abbreviations: HCV, hepatitis C virus; Ig, immunoglobulin; MMP-2, matrix metalloprotease 2; TLR-3, Toll-like receptor 3.

Fabrizi F et al, Am J Kidney Dis 2013

Epidemiology of HCV infection in hemodialysis:

European multicentre study



Jadoul M et al, Nephrol Dial Transplant, 2004

Prevalence of HCV infection in haemodialysis

- CDC USA survey (2002): 7.8%

Finelli L et al, Seminars in Dialysis, 2005

- French survey : 7.7%

Sauné K et al, Nephrol Dial Transplant, 2011

Prevalence of HCV infection in haemodialysis

Clinica Nefrologica con dialisi e trapianto di rene

IRCCS S.Martino-IST Genova

N° pazienti in dialisi: 240

HCV-RNA positivi : 18 (7.5%)

Pattern of HCV infection in haemodialysed patients

- Usually asymptomatic
- Apparently indolent course
- Low transaminases levels
- HCV-RNA fluctuations

Post-transplant outcome in patients with pre-transplant HCV infection

Liver

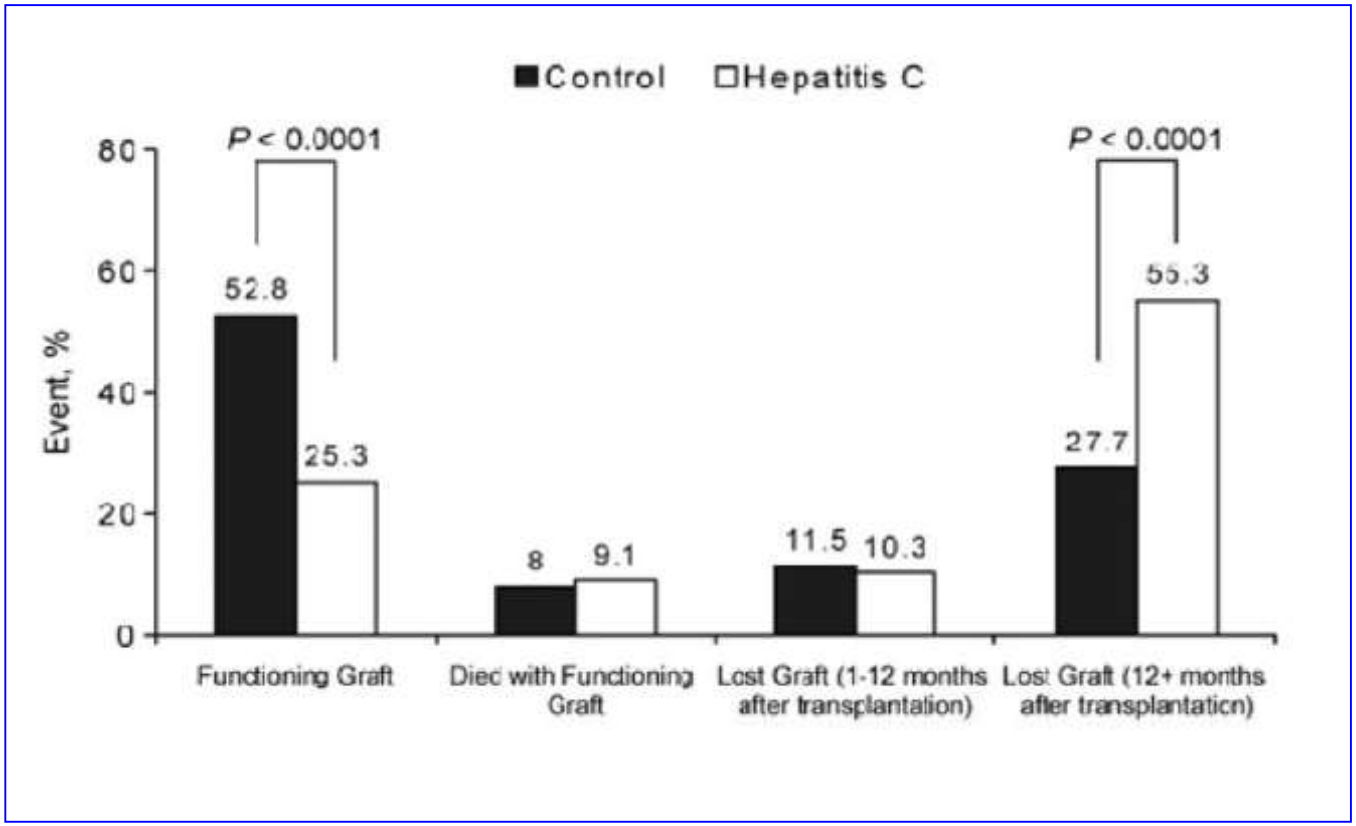
- Greater incidence of increase of transaminases
- Fibrosing cholestatic hepatitis
- Increased viral replication

Kidney

- Glomerulonephritis membranoproliferative with or without cryoglobulinemia
- Acute and chronic transplant glomerulopathy
- Renal thrombotic microangiopathy

Morales JM, Transplantation Proceedings 2004

Effect of chronic hepatitis C on kidney graft function



Weclawiack H et al, Nephrol Dial Transplant 2008

Antiviral therapy

key points

- Limited number of treated patients
- Wide rate of sustained virological response
- Clearance of HCV-RNA after α-IFN therapy is sustained after renal transplantation
- Side-effects are common
- Ribavirin is cleared by the kidneys, causes hemolysis and should be used cautiously
- IFN therapy post-KT is associated with increased rejection of allografts

α-IFN in HCV haemodialysis patients

	SVR	Country
Koenig et al. (1994)	30% (11/37)	Austria
Casanovas-Taltavull et al. (2001)	62% (18/29)	Spain
Degos et al. (2001)	19% (7/37)	France
Kamar et al. (2003)	38% (21/55)	France
Ozdemir et al. (2004)	40% (8/20)	Turkey
Rivera et al. (2005)	40% (8/20)	Spain
Yildirim et al. (2006)	54% (20/37)	Turkey
Buargub et al. (2006)	25.7% (9/35)	Libya
Rocha et al. (2006)	21% (10/46)	Brazil

Only large-size ($n \geqslant 20$ patients) trials were reported.

Martin P et al, J Hepatol 2008

Pegylated Interferon Monotherapy of Chronic Hepatitis C in Dialysis Patients: Meta-Analysis of Clinical Trials

- Sixteen clinical trials (five controlled studies) from 2003 to 2008
- 254 patients
- Sustained virological response: 33%
- Drop-out rate: 23%
- Side effects (interruption of therapy):

- haematological: 18%
- gastrointestinal: 14%

Fabrizi F et al, J Med Virol 2010

Monotherapy with Pegylated Interferon Alpha-2a in Hemodialyzed Patients with Chronic Hepatitis C

Gabriele Zoppoli, MD; Giovanni Di Maio, MD; Stefania Artioli, MD; Cristina Robaudo, MD; Monica Basso, MD; Francesco Torre, MD; Giuseppe Cannella, MD; Antonino Picciotto, MD

TABLE I. Patients' genotypes and viral load during the study (n = 10).

Patients	Genotype	HCV-RNA (copies/mL)			
		Baseline	12 weeks	End of therapy	End of follow-up
1	1b	1.6×10^6	8.1×10^5		
2	1b	9×10^5	Neg[a]	DO[b] 26 weeks (neg)	Neg
3*	1a	1.9×10^5	Neg	DO 24 weeks (neg)	Pos
4*	1a	3.6×10^4	Neg	Neg	Neg
5*	1b	3.6×10^5	Neg	DO 24 weeks (neg)	Pos
6	1b	1.95×10^6	7.7×10^5		
7*	4	2.25×10^5	3.73×10^4		
8	2a/2c	7.7×10^6	Neg	DO 12 weeks (neg)	Pos
9	2a/2c	4.87×10^5	Neg	Neg	Pos
10*	3a	1.3×10^5	Neg	DO 24 weeks (pos)	

[a]*Defined as <50 IU/mL.*
[b]*Dropout.*
**Patients who needed dose reduction (90 μg/week) within the first 4 weeks for myelotoxicity.*

Dialysis & Transplantation 1-5, 2008

PEG-IFN plus Ribavirin in dialysis patients: meta-analysis of clinical trials

- Ten clinical studies (one controlled trial) from 1998 to 2010
- 151 patients
- Sustained virological response: 56%
- Drop-out rate: 25%
- Side effects (interruption of therapy):

- anemia: 26%
- heart failure: 9%

Fabrizi F et al, J Viral Hepatitis 2011

First-generation DAAs and renal impairment

Boceprevir and Telaprevir in renal patients

- BOC and TVR undergo extensive hepatic metabolism:
- *BOC by aldoketoreductase (AKR) and cytochrome P450*
- *TVR by cytochrome P450*
- Main route of elimination is via the feces with minimal urinary excretion
- No dose adjustment of BOC or TVR is required in patients with renal insufficiency

2011 Practice Guideline by the AASLD, Hepatology 2011

PEG-IFN/RBV/Boceprevir or Telaprevir

Author	Dumortier *et al.* [11]	Wiegand *et al.* [12]	Patel *et al.* [13]	Knapstein *et al.* [14]	de Kanter *et al.* [15]	Kaya *et al.* [16]
Year	2013	2014	2014	2014	2014	2015
Patients, n	4	7	16	1	1	5
Age, years	47.5	51	55.1	28	53	44.4
Male, n	2	5	12	1	1	3
Country	France	Germany	USA	Germany	The Netherlands	Turkey
Antiviral therapy	Peg-IFN-α2a (n = 3) or α2b (n = 1) + ribavirin + telaprevir	Peg-IFN-α 2a + ribavirin + telaprevir	Peg-IFN-α 2a + ribavirin + telaprevir (n = 9) or boceprevir (n = 7)	Peg-IFN-α 2a + ribavirin + boceprevir	Peg-IFN-α 2a + ribavirin + telaprevir	Peg-IFN-α2a + ribavirin + telaprevir
HCV genotype	1b	1	1	1b	1	1
Dropouts, n	0	1	2	0	0	1
RVR, n	3	6	6	Yes	Yes	4
SVR, n	NA	6	7	Yes	Yes	4
Antiviral therapy, length	12 weeks	10–12 weeks (triple therapy) + dual therapy (total duration 24–48 weeks)	Up to 48 weeks	32 weeks (triple therapy) + 12 weeks (dual therapy)	12 weeks (triple therapy) + 12 weeks (dual therapy)	24 weeks
Dropout, reason	NA	Anemia	Non-compliance (n = 1), loss to f-u (n = 1)	NA	NA	Dyspepsia
Protease inhibitor, dose	Telaprevir, 750 mg x3/day	Telaprevir, NA	Telaprevir, 750 mg x3/day Boceprevir, 800 mg x3/day	Boceprevir, 800 mg x3/day	Telaprevir, 750 mg x3/day	Telaprevir, 750 mg x3/day
Prior antiviral status, n	Not responders to peg-IFN + RBV (n = 4)	Naïve (n = 4)	Naïve (n = 11)	Naïve	Naïve	Relapser (n = 5)

Second-generation DAAs and renal impairment

Chronic Kidney Disease stages

Stage	GFR
Stage 1	≥90 mL/min/1.73 m^2
Stage 2	60–89 mL/min/1.73 m^2
Stage 3	30–59 mL/min/1.73 m^2
Stage 4	15–29 mL/min/1.73 m^2
Stage 5	<15 mL/min/1.73 m^2

GFR = glomerular filtration rate

According to CKD stages in the Kidney Disease Improving Global Outcomes (KDIGO) guidelines

Sofosbuvir

- The drug is eliminated mainly through renal excretion (2.4% of Sofosbuvir, 3.7% of GS-566500, 67% of GS-331007)

Renal clearance is the major elimination pathway for GS-331007 (predominant circulating metabolite), with a large part actively secreted. The safety and efficacy of SOF has not been established in HCV patients with severe renal impairment or ESRD

Vallet-Pichard et al, Clin Res Hepatol Gastroenterol 2013

SMV distribution and metabolism

Distribution and elimination

- Extensively bound to plasma proteins (>**99.9%**)
  - Primarily albumin and to a lesser extent AAG
- Elimination occurs via biliary excretion, **91% via feces**
  - Minimal excretion into **urine** (**1%**)
- Apparent elimination half-life about 10–41 hours after single-dose administration

Metabolism

- **Substrate and mild inhibitor of CYP 3A system**
- No or weak in-vitro inhibition of CYP 1A2, CYP 3A4, CYP 2C8, CYP 2C19,
- **Mild in-vivo inhibition of CYP 1A2, intestinal CYP 3A4**,
  - No inhibition of CYP 2C9, CYP 2C19, CYP 2D6
- **In-vitro substrate of P-gp and OATP1B1/3**

AAG: alpha 1-acid glycoprotein
CYP: cytochrome P450; P-gp: P-glycoprotein
OATP: organic anion-transporting polypeptide

Daclatasvir

- DCV can be given in subjects with renal impairment including ESRD (stage 5) without dose modification

Although the AUC values were increased by 1.3, 1.9 and 2.1 times in pts with stage 3, 4, 5 respectively, no discontinuation of treatment due to adverse effects were reported, and all adverse effects were mild in intensity

Garimella T et al, J Viral Hepatitis 2014

Asunaprevir

Is eliminated by hepatic metabolism, biliary excretion and direct intestinal secretion. Minimal renal excretion

Eley T et al, Antiviral Therapy 2014

Pharmacokinetics largely comparable in 24 adult subjects who had either normal renal function or ESRD.
Dosage adjustment may not be required in subjects with renal impairment

Garimella T et al, AASLD 2013

Urgent treatment with Sofosbuvir based regimen for HCV G1 patients with severe renal insufficiency

- 4 male pts (2 G1a)
- 2 cirrhotic on dialysis, 1 OLT recipient with FCH on dialysis, 1 post liver-kidney transplant requiring intense immunosuppressive therapy for kidney rejection)
- Therapy: Sofusbuvir + Simeprevir (in one pt SOF + RIBA)

	Age	Gender	HCV Gt	Agents	HD	Urgency	Outcome
Patient 1	62	M	1a	Sof 400 daily + Riba 200 every other day	Y	FCH post LT	SVR 24
Patient 2	53	M	1b	Sof 400mg every other day + sim 150 daily	N	Intense immunosuppression post LKTx	EOT
Patient 3	54	M	1a	Sof 400mg every other day + sim 150 daily	Y	Pre-transplant with normal hepatic synthetic function	Week 4 (169 IU)
Patient 4	64	M	1b	Sof 400mg every other day + sim 150 daily	Y	Pre-transplant with normal hepatic synthetic function	Week 4 (UND)

Bhamidimarri KR et al, AASLD 2014 pp 688-689

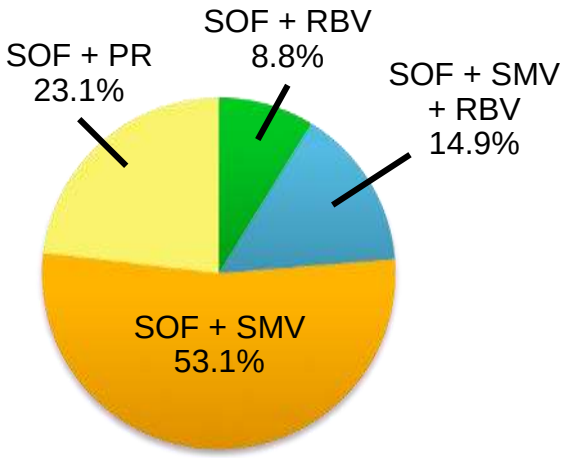
Safety, antiviral efficacy and pharmacokinetics (PK) of Sofosbuvir in patients with severe renal impairment

- 10 pts (G1 or 3)
- CrCl < 30mL/min (not on dialysis)
- Therapy: SOF 200 mg + RIBA 200 mg daily for 24 w
- Renal function stable

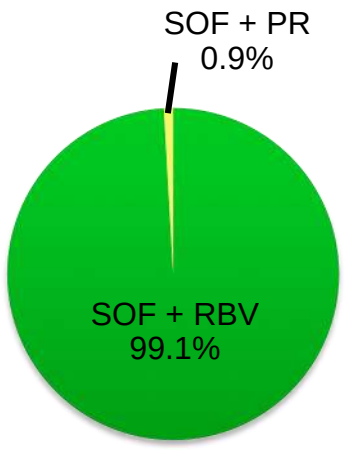
Gane EJ, AASLD 2014, pp 667

HCV-TARGET: Observational Study of Real-World Outcomes With DAAs

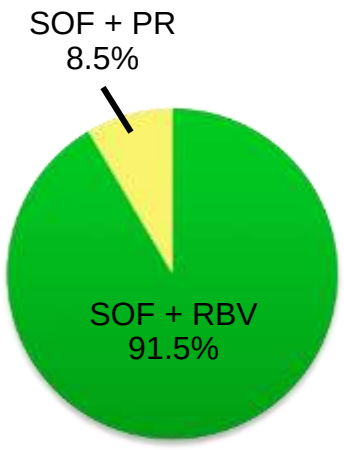
- HCV-TARGET: longitudinal, observational study involving 38 academic and 15 community medical centers in the United States, Germany, and Canada
- Current analysis includes data from 2063 sequentially enrolled pts receiving SOF-based regimens
- IFN-free regimens dominate treatment choice



Genotype 1



Genotype 2



Genotype 3

Jensen D, et al. AASLD 2014. Abstract 45.

HCV TARGET: Real-World Analysis of SOF Regimens in Pts With Renal Dysfunction

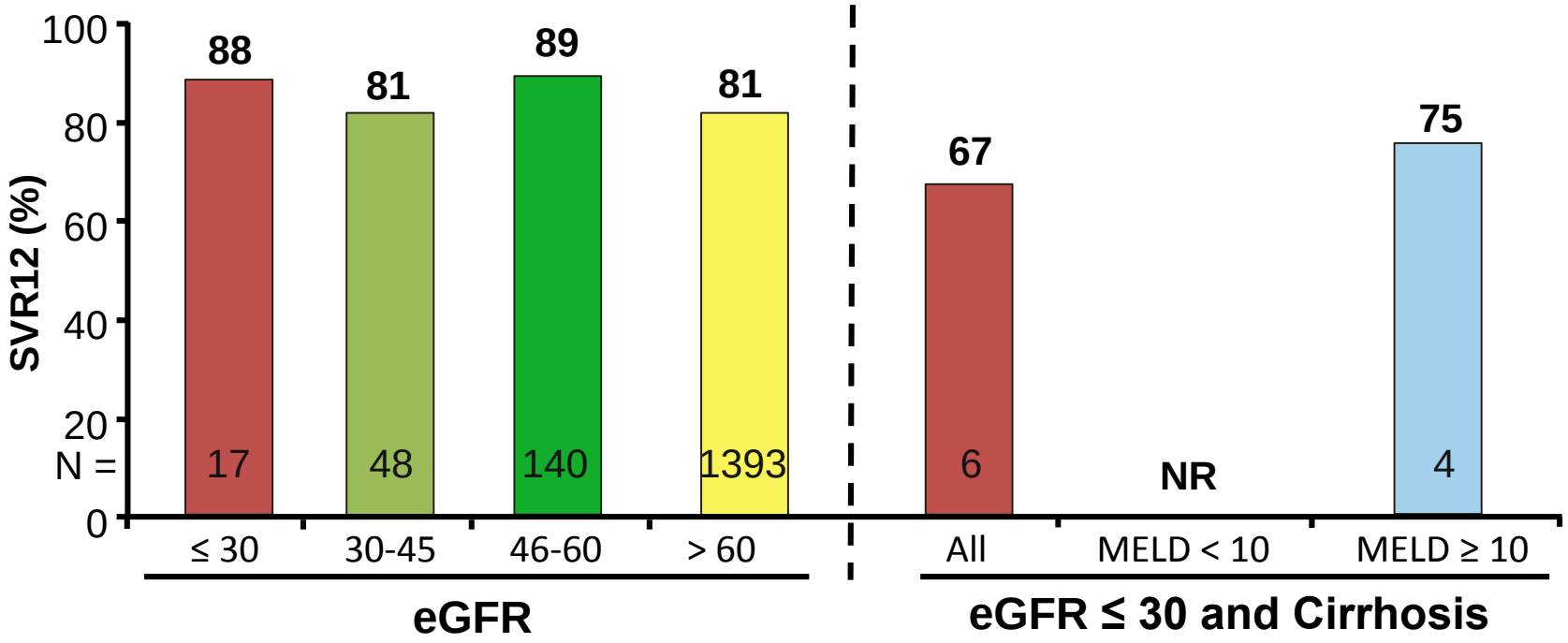
- Analysis evaluated safety, efficacy of sofosbuvir-containing regimens by BL renal function in 1893 sequentially enrolled pts
  - Sofosbuvir use with eGFR < 30 mL/min/1.73m^2 is off label

Baseline Characteristic	eGFR ≤ 30 (n = 19)	eGFR 31-45 (n = 63)	eGFR 46-60 (n = 168)	eGFR > 60 (n = 1643)
Presence of cirrhosis, n (%)	8 (42)	43 (68)	95 (57)	844 (51)
▪ History of decompensation	6 (32)	30 (48)	55 (33)	380 (23)
▪ MELD ≥ 10	5 (26)	26 (41)	33 (20)	227 (14)
HCC, n (%)	1 (5)	16 (25)	34 (20)	160 (10)
Mean total bilirubin, mg/dL (range)	2.1 (0.2-21)	1.6 (0.2-22)	1.0 (0.1-8.0)	1 (0.1-15)
Mean albumin, g/dL (range)	3.6 (2.5-5.0)	3.7 (1.8-5.0)	3.8 (2.0-5)	3.9 (1.2-5)
Mean platelets x 10^3/μL (range)	145 (38-267)	142 (37-306)	162 (42-595)	155 (14-567)
Mean INR (range)	1.1 (0.9-1.4)	1.2 (0.9-4.0)	1.2 (0.9-3.0)	1.1 (0.7-4.0)

Saxena V, et al. EASL 2015. Abstract LP08.

HCV TARGET: SVR12 With SOF Regimens by Baseline *eGFR* and Cirrhosis Status

- Sofosbuvir + simeprevir most common regimen used
- Overall SVR12 rates high and similar (> 80%) across renal function strata in pts with known treatment outcome



Saxena V, et al. EASL 2015. Abstract LP08. Reproduced with permission.

HCV TARGET: Safety Outcomes With SOF Regimens by Baseline eGFR

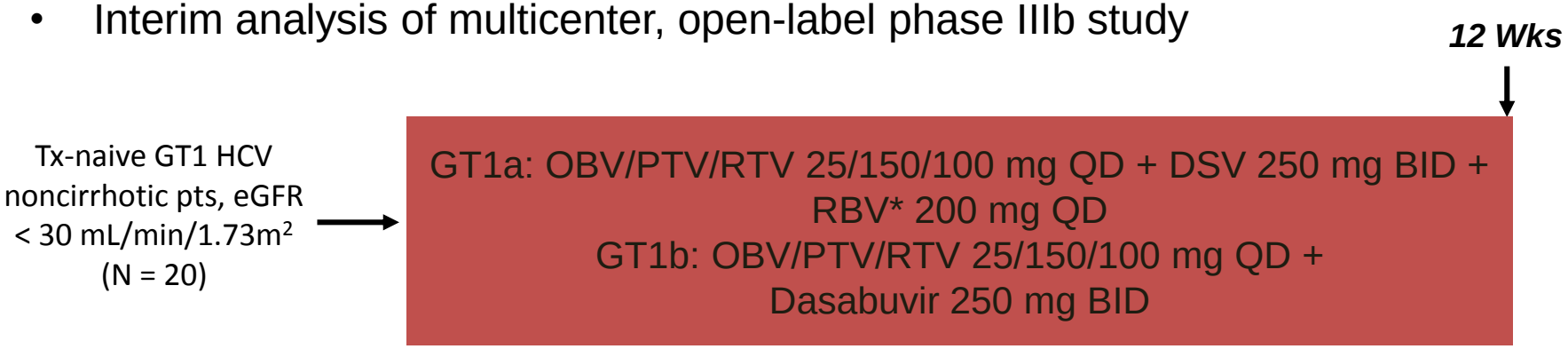
- Rates of anemia AEs, worsening renal function, and renal and urinary AEs increased across decreasing eGFR strata

Safety Outcome in Pts Who Completed SOF-Containing Therapy	eGFR ≤ 30 (n = 17)	eGFR 31-45 (n = 56)	eGFR 46-60 (n = 157)	eGFR > 60 (n = 1559)
Anemia AEs	6 (35)	16 (29)	37 (24)	246 (16)
▪ Transfusions	2 (12)	5 (9)	3 (2)	31 (2)
▪ Erythropoietin	1 (6)	8 (14)	14 (9)	50 (3)
▪ Reduction in RBV dose*	3 (38)	8 (30)	33 (42)	185 (19)
▪ RBV discontinuation	0	4 (15)	1 (1)	12 (1)
Worsening renal function	5 (29)	6 (11)	4 (3)	14 (1)
Renal or urinary system AEs	5 (29)	6 (11)	13 (8)	84 (5)
Serious AEs	3 (18)	13 (23)	8 (5)	100 (6)
Cardiac AEs	1 (6)	2 (4)	8 (5)	53 (3)

Saxena V, et al. EASL 2015. Abstract LP08.

RUBY-1: OBV/PTV/RTV + DSV ± RBV in Tx-naive, Noncirrhotic GT1 Pts With CKD

- Interim analysis of multicenter, open-label phase IIIb study



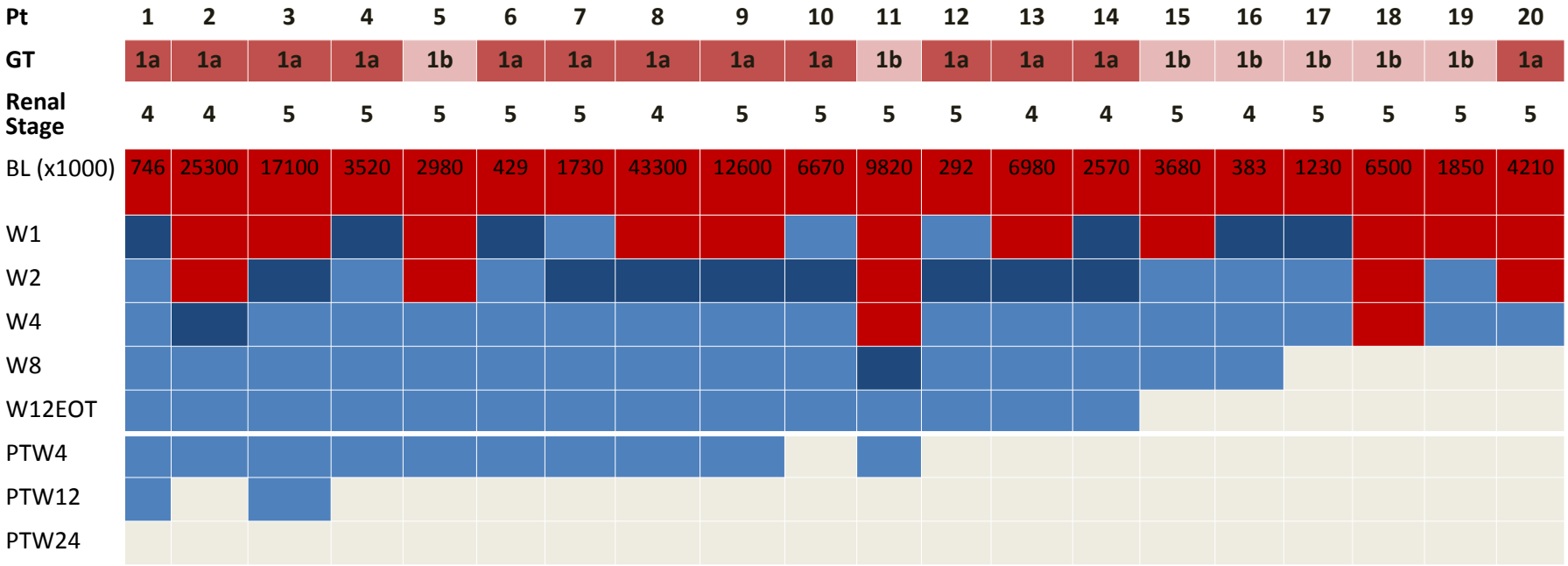
*RBV management for pts with GT1a HCV infection: RBV dosed 4 hrs before hemodialysis in hemodialysis pts; wkly Hb assessment in Mo 1 and then Wks 6, 8, 12; RBV suspended in pts with > 2 g/dL decline in Hb in < 4 wks or Hb < 10 g/dL; RBV dosing resumed at clinician's discretion if Hb normalized.

- Key baseline characteristics
  - F2 fibrosis: 30%
  - F3 fibrosis: 20%
  - CKD stage 4 (*eGFR* 15-30): 35%
  - CKD stage 5 (*eGFR* < 15): 65%
  - 65% of pts on hemodialysis

Pockros PJ, et al. EASL 2015. Abstract L01.

RUBY-1: Virologic Efficacy

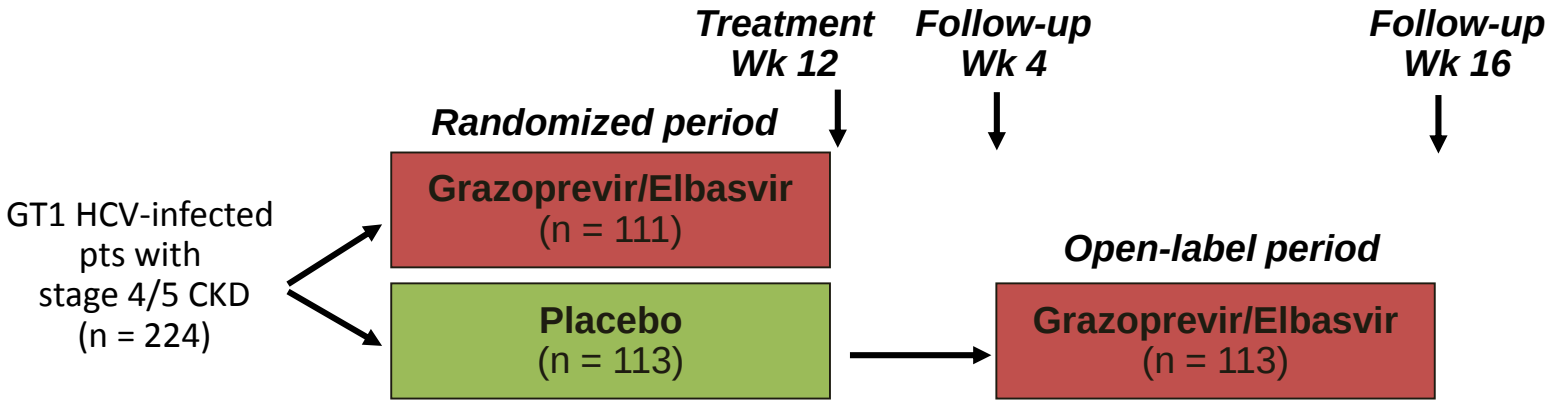
- SVR4: 10/10 pts reaching posttreatment Wk 4
  - SVR12: 2/2 pts reaching posttreatment Wk 12
  - No virologic failures observed as of time of reporting



Pockros PJ, et al. EASL 2015. Abstract L01. Reproduced with permission.

C-SURFER: Grazoprevir/Elbasvir in Pts With GT1 HCV and Stage 4 or 5 CKD

- Multicenter, part-randomized, parallel-group, placebo-controlled, phase III trial

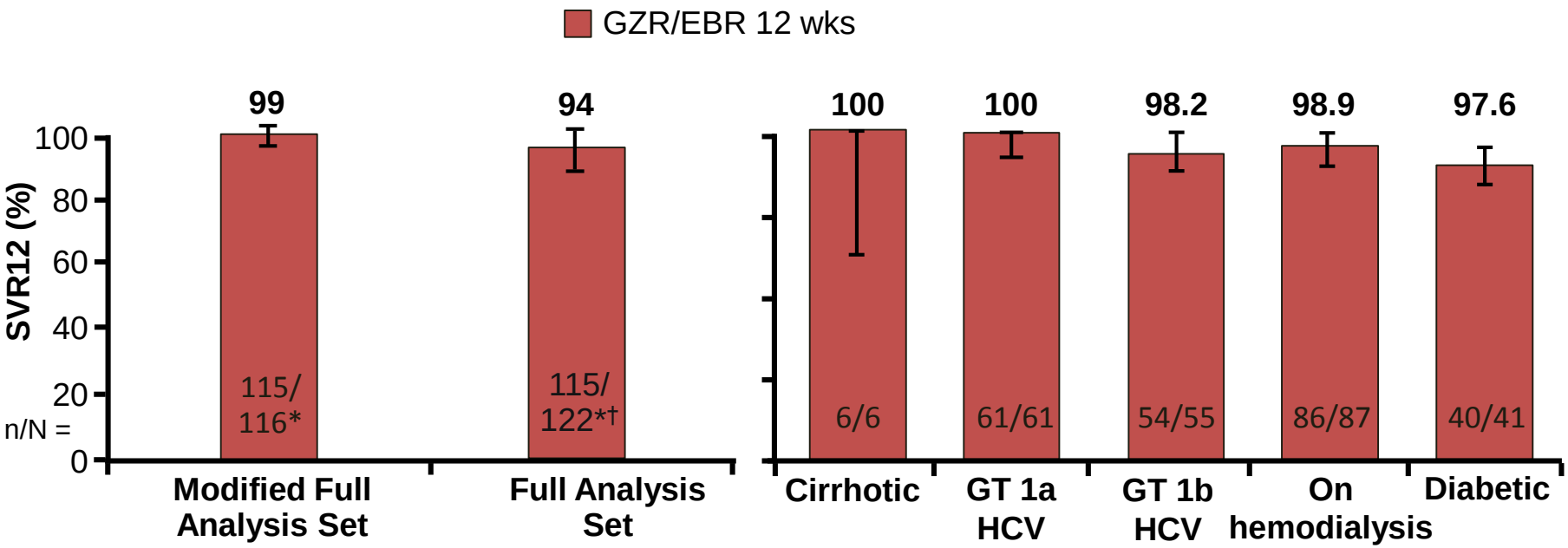


Grazoprevir/elbasvir dosed orally 100 mg/50 mg once daily. This study also included a pharmacokinetic analysis (n = 11) in which pts were treated as in the randomized grazoprevir/elbasvir study group.

- Treatment arms well matched at baseline
  - Pts split evenly by GT1a and 1b infection (52% for GT1a); 6% had compensated cirrhosis
  - 75% and 77% were on hemodialysis; 32% to 36% were diabetic
  - 81% and 82% were CKD stage 5 (eGFR < 15 mL/min/1.73 m^2, or on hemodialysis); 18% and 19% were CKD stage 4 (eGFR 15-29 mL/min/1.73 m^2)

Roth D, et al. EASL 2015. Abstract LP02.

C-SURFER: Efficacy Results



Modified analysis set: pts in pharmacokinetic substudy and pts randomized to immediate treatment who received ≥ 1 drug dose; excludes pts who died or discontinued where cause not related to study treatment.
Full analysis set: all pts receiving ≥ 1 drug dose.
*1 pt relapsed on each arm.
†6 pts in the full analysis set discontinued unrelated to treatment: lost to follow-up (n = 2), n = 1 each for death, noncompliance, withdrawal by subject, and withdrawal by physician (owing to violent behavior).

Roth D, et al. EASL 2015. Abstract LP02.

C-SURFER: Adverse Events

AE, %	Grazoprevir/Elbasvir (Randomized Treatment) (n = 111)	Placebo (n = 113)
Serious AEs	14.4	16.8
Discontinuation due to AE	0	4.4
Death	0.9	2.7
Common AEs*	75.7	84.1
▪ Headache	17.1	16.8
▪ Nausea	15.3	15.9
▪ Fatigue	9.9	15.0
▪ Insomnia	6.3	10.6
▪ Dizziness	5.4	15.9
▪ Diarrhea	5.4	13.3
Hb grade decrease from baseline		
▪ 1 grade	24.3	26.5
▪ 2 grades	12.6	7.1
▪ 3 grades	3.6	1.8
▪ 4 grades	0	0.9

*Reported in ≥ 10% of pts in either arm.

Roth D, et al. EASL 2015. Abstract LP02. Reproduced with permission.

Current DAA clearance

Antiviral agent	Dose	Clearance
Boceprevir	800 mg x3/day	< 10% renal route
Telaprevir	750 mg x3/day	1% renal route
Sofosbuvir	400 mg/day	81% renal route
Simeprevir	150 mg/day	< 1% renal route
Grazoprevir/Elbasvir	100/50 mg daily	< 1% renal route
3D regimen: ombitasvir, paritaprevir/ritonavir and dasabuvir	25/150/100 mg once daily and 250 mg x2/day	< 2% renal route
Ledispavir	90 mg daily	< 1% renal route
Daclatasvir	30 mg twice daily	< 10% renal route
Asunaprevir	200 mg twice daily	< 10% renal route
Beclabuvir	75 mg twice daily	< 10% renal route

Fabrizi F et al, Expert Rev Clin Pharmacol 2015

Punti chiavi

- L’infezione da HCV in pazienti sottoposti ad emodialisi si può stimare al di sotto del 10%
- L’infezione da HCV in questi pazienti si associa a maggiore mortalità e a ridotta qualità della vita
- I DAA forniscono in questo contesto clinico un ottimo rapporto costo/beneficio (a parte l’aspetto economico)
- E’ ipotizzabile il loro impiego indipendentemente dall’inserimento in lista per trapianto di rene