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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Ashley Brown	Acts in a consultancy capacity for and/or as a speaker at company sponsored events for and/or received personal grants for attending conferences from, the following companies: Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, Merck Sharpe & Dohme, Novartis, Roche.
Date	**22 September 2012**

Imperial College London

Imperial College Healthcare NHS Trust

Treating Hepatitis C in Patients with Chronic Renal Disease

Dr Ashley Brown, Consultant Hepatologist
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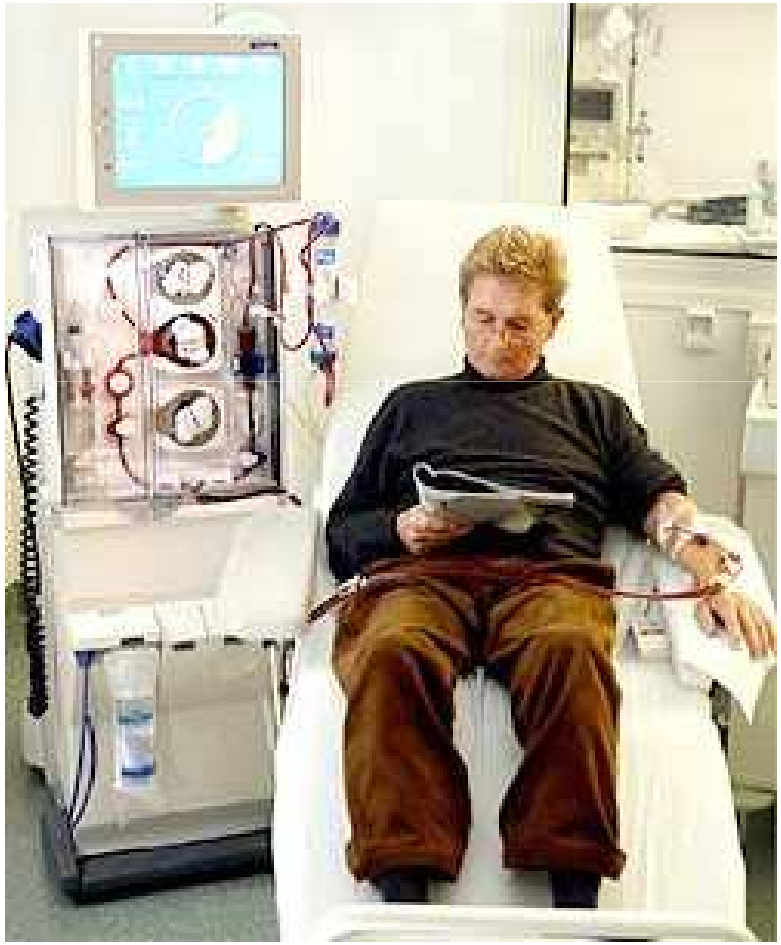
Relationship between HCV and End Stage Renal Disease

Patterns of HCV prevalence and seroconversion in haemodialysis units

- A prospective, observational study of adult hemodialysis patients randomly selected from 308 representative dialysis facilities in France, Germany, Italy, Japan, Spain, the UK and the USA.
- Mean HCV prevalence was 13.5% (2.6% to 22.9%)
- Increased HCV prevalence was associated with longer time on dialysis, male gender, black race, DM, HBV infection, prior renal transplant, and alcohol or substance abuse in the previous 12 months.
- HCV seroconversion was associated with longer time on dialysis, HIV/AIDS, HBV infection, and recurrent cellulitis/gangrene.

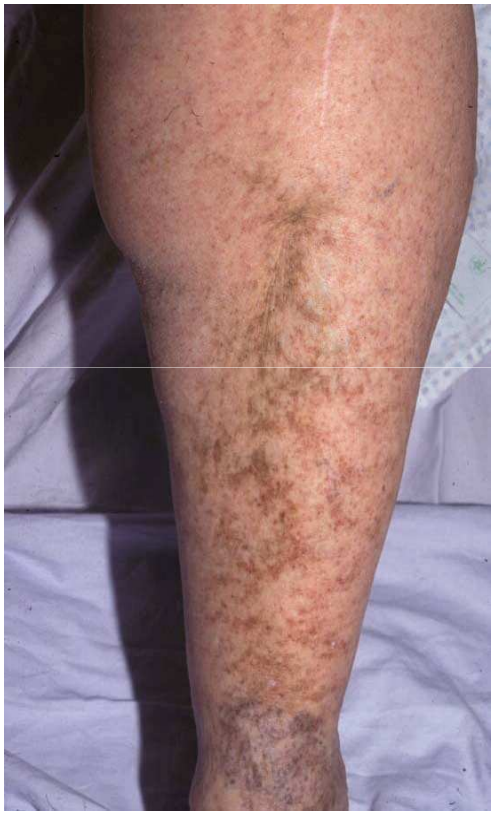
Fissell *et al., Kidney Int*. 2004 Jun;65(6):2335-42

Why is HCV prevalent on Dialysis Units?



- Multiple previous transfusions pre 1990
- Cross contamination of lines and equipment
- Higher incidence of HT and DM among ethnic groups where HCV is more prevalent
- Cryoglobulinaemia as an extrahepatic manifestation of HCV
- ‘Dialysis holidays’
- Live donor transplants overseas

HCV and Cryoglobulinemia



- Occurs in dependent areas
- Deposition of cryoglobulins in small capillaries
- Ulcerations may develop
- Pruritic

ESRD and dialysis in HIV-positive patients: a long-term cohort study with 22y follow-up

- 9198 patients (78.2% male, 88.9% Cauasian) followed over three time periods: 1989-1996 (pre-HAART), 1997-2003 (early HAART) and 2004-2010 (late HAART).
- 9198 patients [78.2% male; 88.9% Caucasian)
- Risk factors for ESRD were:
  - Black ethnicity (RR 5.1; 95% CI 2.3-10.3; P < 0.0001],
  - Injecting drug use (RR 2.3; 95% CI 1.1-4.6; P = 0.02)
  - HCV coinfection (RR 2.2; 95% CI 1.1-4.2; P = 0.03).
- The incidence of ESRD increased in Caucasian patients (from 29.9 to 41.0 and 43.4 per 100 000 PYFU, respectively.
- The prevalence of ESRD increased over time and reached 1.9 per 1000 patients in 2010.
- ESRD was associated with a high overall mortality (RR 9.9; 95% CI 6.3-14.5; P < 0.0001)

Bickel et al., 2012 Sep 20. [Epub ahead of print]

RRT in Patients With HIV in a European Region

- A cross-sectional study to identify characteristics of HIV patients receiving RRT in Sept 2011 in Andalusia. 48 of 8744 patients were on RRT had HIV infection (prevalence 0.54%). 27 (56.3%) had HCV coinfection.

RRT Method	HIV-Positive	HIV-Negative
Haemodialysis	81.3%	46.8%
Peritoneal Dialysis	2%	4%
Renal Transplant	16.7%	49.2%

- Only 3 patients (7.5%) were on the waiting list for renal transplantation.

Mazuecos *et al.,* Transplant Proc. 2012 Sep;44(7):2053-6

Renal Transplant Outcomes in Patients with HIV

- A retrospective cohort study of HIV-positive patients receiving renal transplants in the era of HAART.
- From 2001-2011, 10 HIV-infected patients received a renal transplantation (median follow-up 40.5 months).
- Only two patients presented acute rejection, all remain alive and the graft survival was 100% in the first and third years post-transplant.
- Demographic and comorbidity variables showed no difference between patients transplanted or included on the waiting list (n = 12) and patients excluded and never transplanted (n = 36).

Mazuecos *et al.,* Transplant Proc. 2012 Sep;44(7):2053-6

Benefits of treating HCV

Survival Benefit of HCV Treatment

- Interferon treatment reduces risk of death, transplantation, and complications of cirrhosis

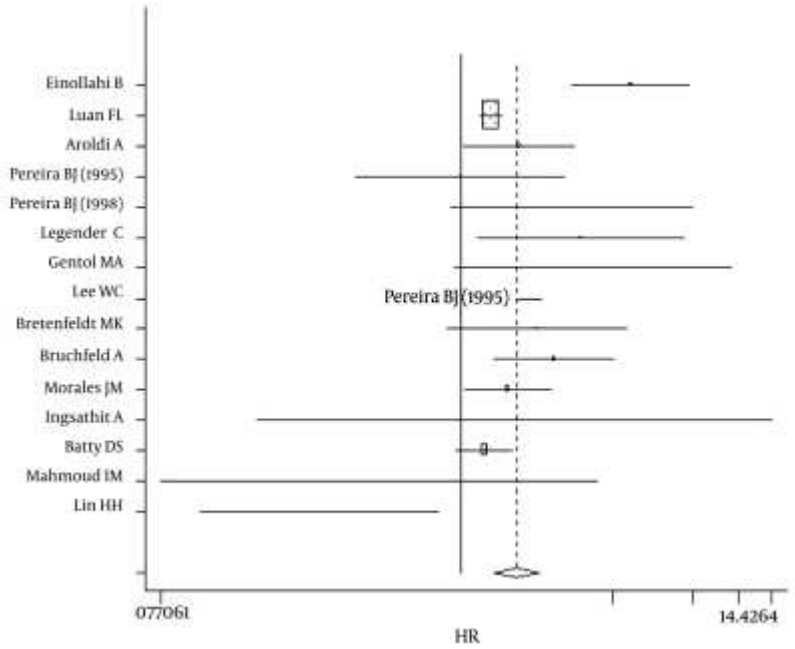
Risk Factors for Survival (Multivariate Cox Regression Analysis)		
Survival Outcome	**Risk Ratio**	**95% Confidence Interval**
Interferon therapy vs no therapy		
• Death and liver transplantation	0.5*	0.3-0.9
• Death, liver transplantation, and complications	0.5*	0.3-0.7
• Development of HCC	0.7	0.2-2.7

Niederau C, et al. Hepatology. 1998;28:1687-1695.

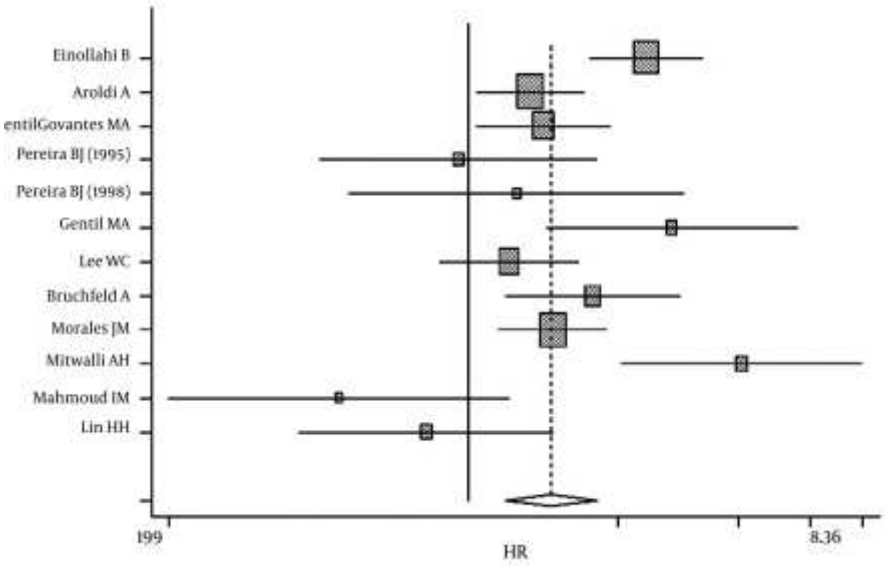
HCV reduces both patient and graft survival in Renal Transplant Recipients

Authors/Year/Country	No pats/HCV+	RT	PS/GS	Type of Study
Einollahi et al. (2003) Iran	1006/45	Yes/yes	Retrospective cohort	
Luan et al. (2008), U.S	79337/3708	Yes/no	Retrospective cohort	
Aroldi et al. (2005) Italy	541/209	Yes/yes	Retrospective cohort	
Legendre et al. (1998) France	499/112	Yes/no	Retrospective cohort	
Gentil et al. (1999) Spain	320/85	Yes/yes	Retrospective cohort	
Lee et al. (2001) Taiwan	477/136	Yes/yes	Retrospective cohort	
Breitenfeldt et al. (2002) Ger.	927/123	Yes/yes	Retrospective cohort	
Bruchfeld et al. (2004) Sweden	571/51	Yes/no	Retrospective cohort	
Morales et al. (2004) Spain	3365/488	Yes/yes	Retrospective cohort	
Ingsathit et al. (2007) Thailand	346/22	Yes/no	Retrospective cohort	
Batty et al. (2001) U.S	28692/1624	Yes/no	Retrospective cohort	
Mahmoud et al. (2004) Egypt	133/80	Yes/yes	Retrospective cohort	
Lin et al. (2004) Taiwan	299/129	Yes/yes	Retrospective cohort	
Ridruejo et al. (2007) Argentina	396/155	Yes/yes	Retrospective cohort	
Gentil Govantes et al. (2009) Sp.	5693/1053	No/yes	Retrospective cohort	
Mitwalli et al. (2006) Saudi Arabia	448/286	No/yes	Retrospective cohort	
Pereira et al. (1995) U.S.	75/19	Yes/yes	Clinical trial	
Pereira et al. (1998) U.S	103/23	Yes/yes	Clinical trial	

HCV reduces both patient and graft survival in Renal Transplant Recipients



Patient Survival
(Combined Hazard Ratio 1.69)



Graft Survival
(Combined Hazard Ratio 1.56)

Impact of HCV on survival in dialysis patients: a link with cardiovascular mortality?

- Meta-analysis of 14 observational studies involving 145 608 unique patients on long-term dialysis.
- Pooling of study results demonstrated that anti-HCV antibody was an independent and significant risk factor for death.
- The summary estimate for adjusted relative risk (all-cause mortality) was 1.35 with a 95% confidence interval (CI) of 1.25-1.47.
- Stratified analysis showed that the adjusted RR for liver disease-related death was 3.82 (95% CI, 1.92; 7.61); the adjusted RR for cardiovascular mortality was 1.26 (95% CI, 1.10; 1.45).

Fabrizi et al., J Viral Hepat. 2012 Sep;19(9):601-7.

Assessment of HCV in Renal Patients

Why not treat HCV in all dialysis patients?

- Not all patients need treatment - the natural history of HCV is a variable, but generally slowly progressive one. Many patients will never develop cirrhosis and its associated complications.

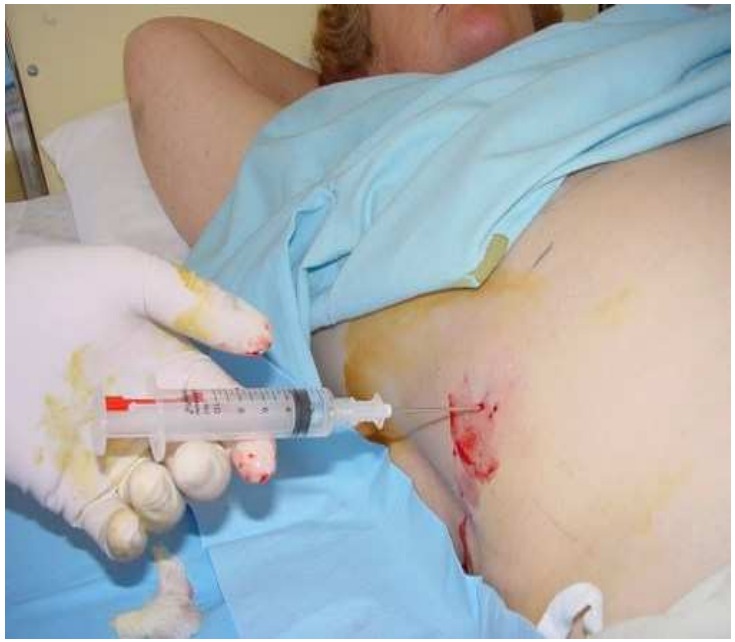
- Dialysis patients with multiple comorbidities may tolerate treatment poorly with limited success rate

- However all HCV positive patients on dialysis should be ASSESSED for treatment whether or not they are listed for transplantation (and should remain under specialist follow-up)

Factors to consider when making treatment decisions

- Age of patient
- Duration of infection
- Stage of disease
- Comorbidities and concurrent medications
- Transplant status (?LRRT)
- Patients wishes!

Is Liver Biopsy always Necessary?



- The requirement for liver biopsy has been perceived as a deterrent in the past but the development of new, non-invasive techniques for assessment of hepatic fibrosis may prove a more acceptable option for many patients

Is Liver Biopsy always Necessary?

NO

- Patient wants treatment even if no fibrosis
- Patient does not want treatment or treatment contraindicated even if advanced fibrosis

AND

- *Fibroscan*, labs and radiographic studies show no evidence of significant fibrosis

YES

- If there is any ambiguity over the results of *Fibroscan*, labs or radiographic studies

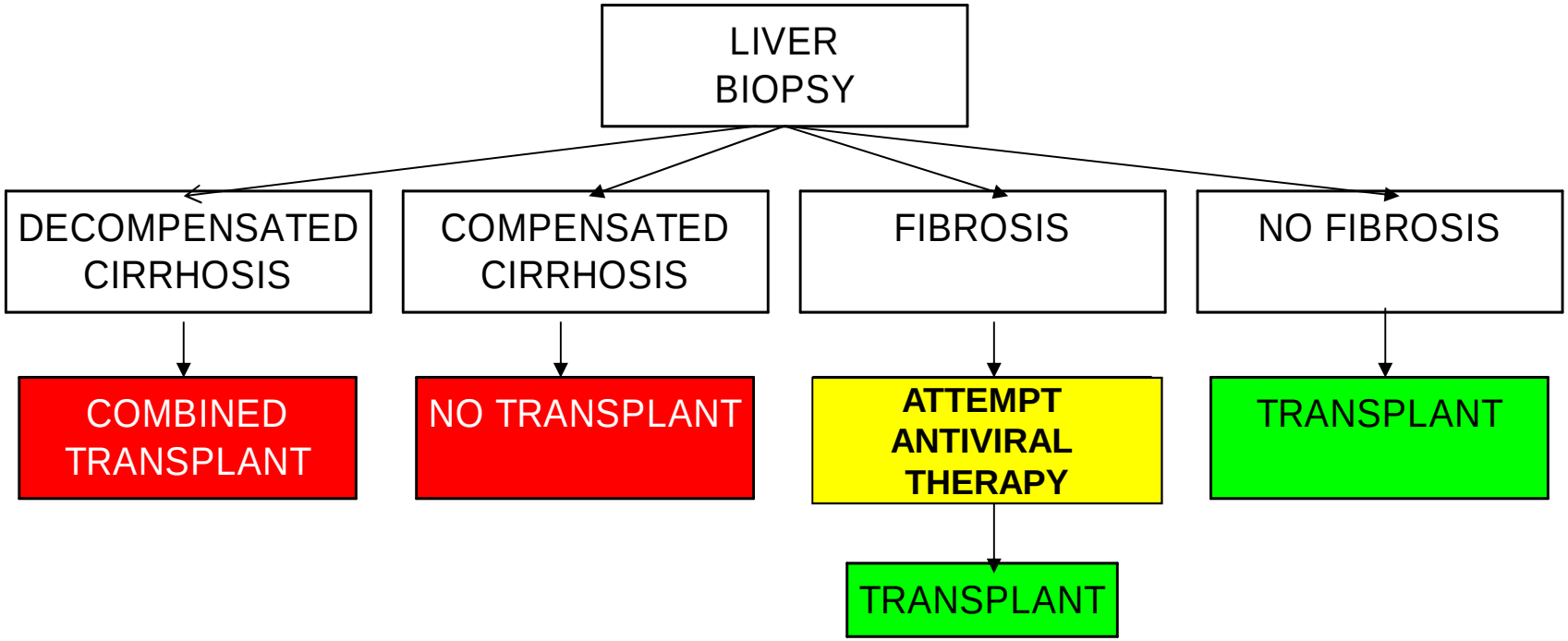
OR

- Patient is considering proceeding to renal transplant without antiviral treatment

OR

- Evidence or suspicion of other liver diseases

Suggested transplant algorithm



Gane & Pilmore, *Transplantation*, . 2002 Aug 27;74(4):427-3

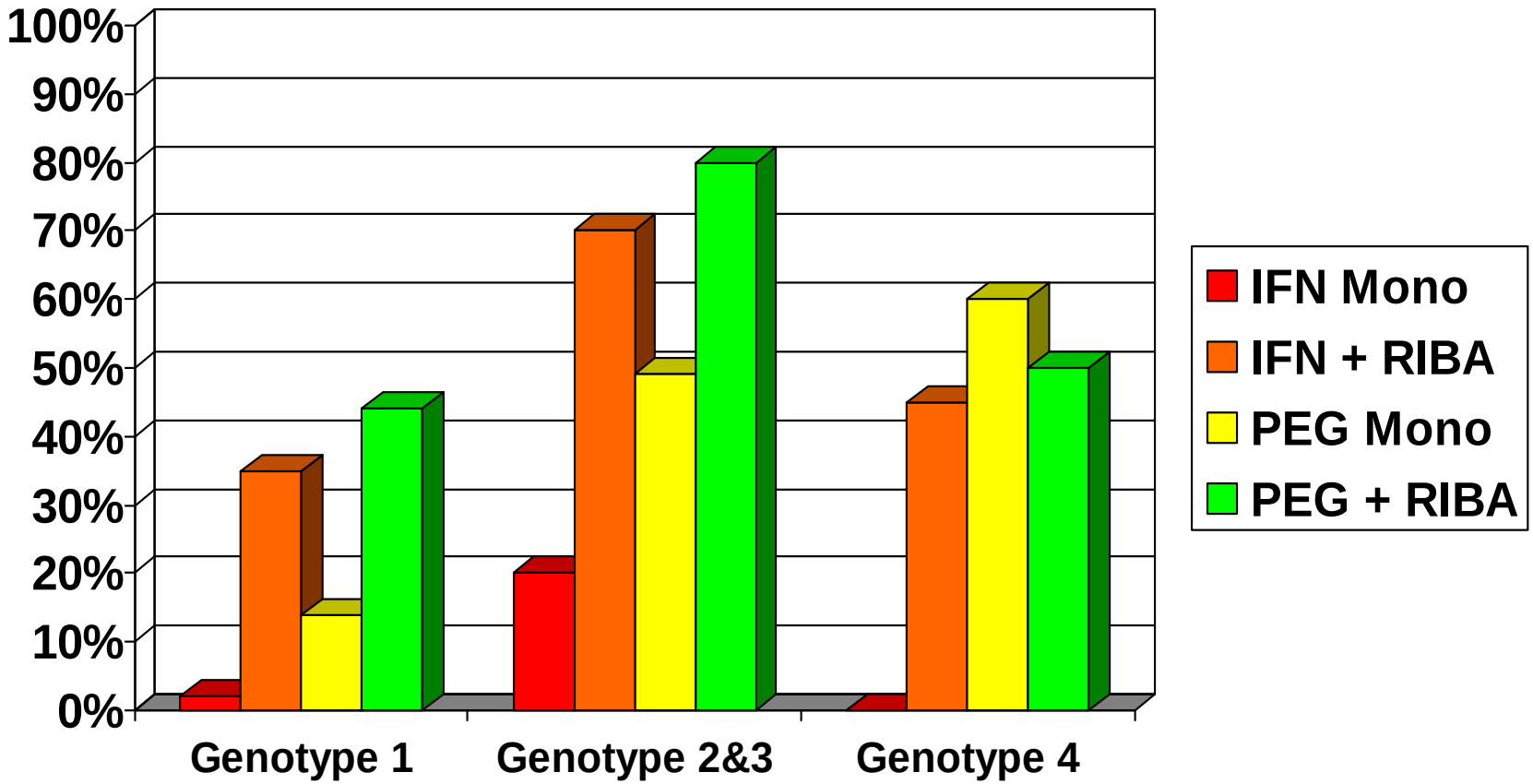
Practicalities of treating HCV

Virological responses to Peg-INF-2a in haemodialysis patients infected with HCV

- 41 treatment-naive HD patients(65.8% male, age range 23-65y) given peg-IFN-α-2a 135 mcg/week for 48 weeks. Biochemical and virological responses were evaluated at treatment weeks 12, 24, 48, and 72.
- 38 of 41 patients completed the treatment
- 60.5% EVR, 63.2% EOTR; 50% SVR
- Only the Knodell histology activity index correlated with SVR (P = 0.048)

Kose et al., Clin Exp Nephrol, 2012 Jul 20. [Epub ahead of print]

Development of Treatment for HCV



Ribavirin

- Mode of action still unclear
- Renal metabolism
- Major side-effect of intravascular haemolysis
- Drug-level monitoring a matter of much debate

AVT in haemodialysed HCV patients: efficacy, tolerance and treatment strategy

- 32 treatment -naïve patients were treated with Peg-IFN-α2a and ribavirin using two different strategies of ribavirin and EPO administration:
  - ADAPTIVE: Start RBV at 600mg/wk and adapting EPO when Hb<10g/dL
  - PREVENTATIVE: Start RBV at 1000mg/wk while increasing EPO from the start

	ADAPTIVE	**PREVENTATIVE**	P value
Median Hb	9.6g	10.9g	0.02
Frequency of Hb<10g	58%	5%	0.0007
Median RBV dose	105mg/d	142mg/d	P<0.0001
Frequency of transfusion	50%	20%	P=0.08

- Compared to patients with normal renal function, ESRD patients had lower ribavirin concentrations during the first month (0.81 vs. 1.7mg/L, P=0.007) and similar concentrations thereafter. SVR was reached in 50%.

Deltenre et al., CHU Lille, Lille, France

St Mary's HD/HCV Treatment Cohort

1	68	M	Acute	4			In work-up
2	32	F	2/6	3a			In work-up
2	66	M	4/6	1a			In work-up
3	59	M	3/6	1b	RO 180	200 tiw	on Rx
4	35	M	Fibro 5.8	1b	RO 180	200 od	on Rx
5	36	M	6/6	1a	RO 180	200 od	SVR12
6	41	M	1/6 2/18	2	RO 180	200od	SVR
7	30	M	3/6 4/18	4	RO 135	200 tiw	SVR
8	29	M	2/6	1b	SP 80	400 od	SVR
9	31	M	Acute	3a	RO 180	200 tiw	SVR
10	55	F	3/6	1a	RO 135	200tiw	SVR
11	33	F	1/6	1b	RO 180	200 od	NR
12	56	M	5/18 3/6	1	RO 180	200 tiw	relapser
13	40	M	Acute	1a	RO 135	200 tiw	relapser
14	48	M	1/6 3/18	3a	RO 180	200 tiw	relapser
15	54	M	2/6	4r	RO 180	200 tiw	relapser
16	42	M	1/6	1a	RO 135	200 tiw	intolerant

Practical Aspects of treating Dialysis Patients

- Ensure patient ‘buy-in’
- Liaise early with nephrologists and discuss EPO usage
- Hepatitis CNS and dialysis nurses liaison
- Consider lower starting dose of RBV
- Close monitoring of Hb with management strategy in place
- Agree futility and ‘plan B’

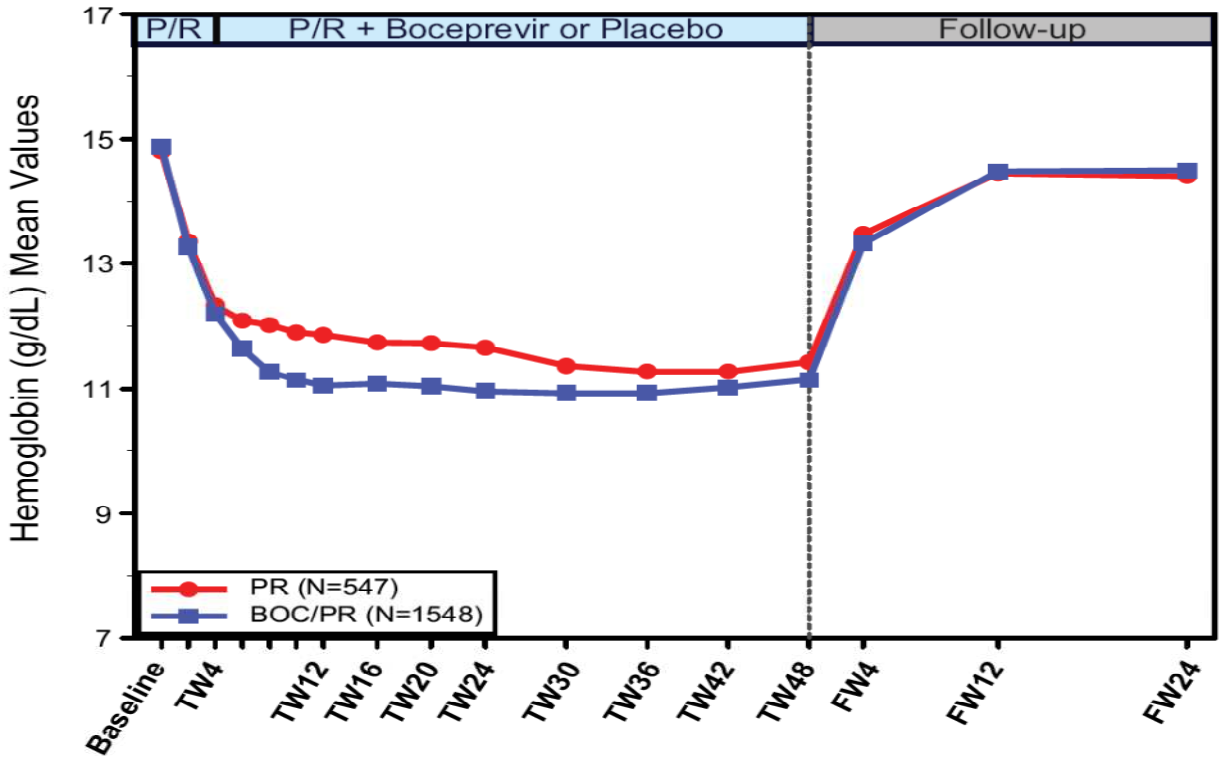
New treatments for HCV

New Treatments for HCV

- Boceprevir and Telaprevir now licensed and available for treatment of HCV
- Significantly improved SVR rate
- Hepatic metabolism so pharmacokinetic properties of BOC and TVR are not altered to a clinically meaningful extent in patients with impaired renal function[1,2].
- No published clinical trials

1. Treitel et al., *Clin Pharmacokinet*. 2012 Sep 1;51(9):619-28; 2. Garg *et al Antivir Ther*. 2012 Sep 7

Protease inhibitors may exacerbate anaemia

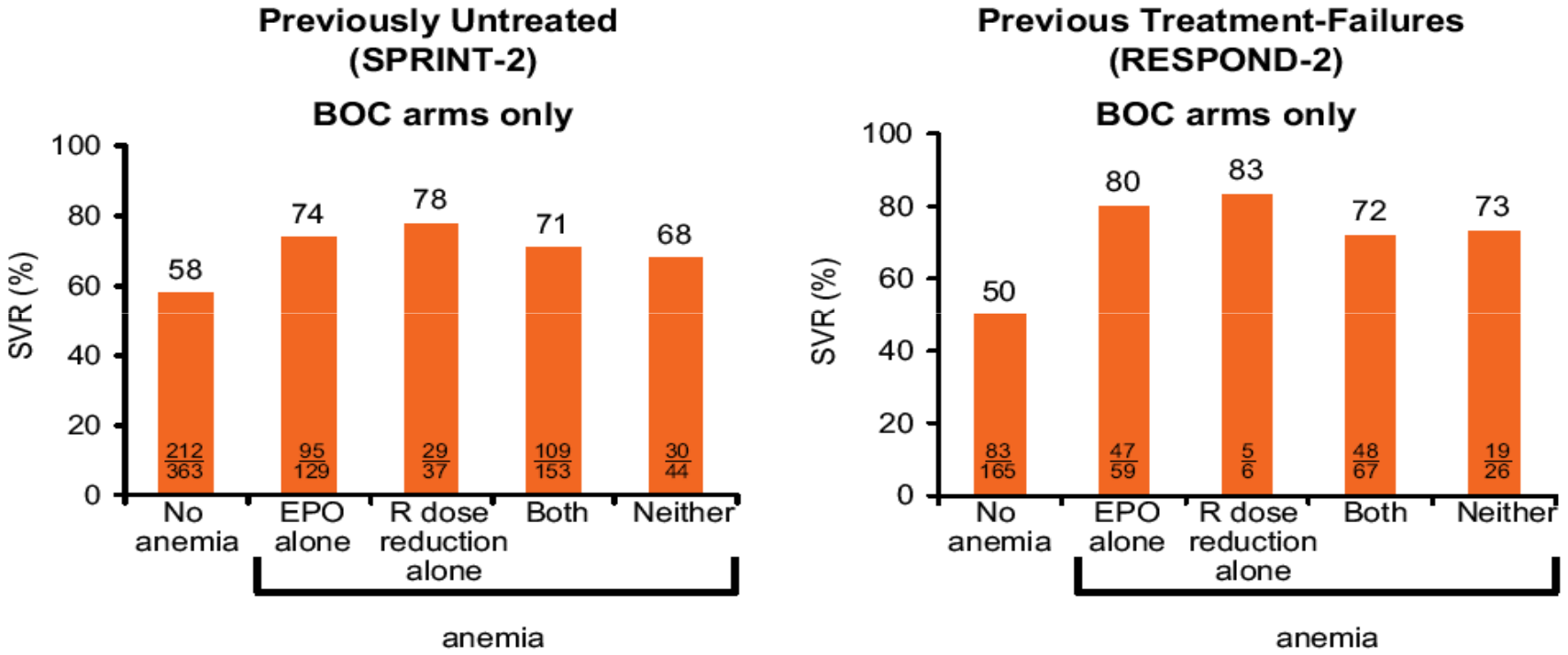


Mean Hb Concentration Over Time By Treatment Arm

(includes phase 2 study of previously untreated patients)

Sulkowski et al., Abstract, AASLD 2011

BOC-associated anaemia may be managed by RBV dose-reduction without affecting SVR



- SVR rate in patients managed with RBV dose reductions alone were comparable to those in patients managed with EPO, with or without RBV dose reduction

Sulkowski et al., Abstract, AASLD 2011

Treatment of HCV after renal transplantation

Treatment of HCV after renal transplant

- In the setting of powerful immunosuppression, HCV replication can sharply increase, after renal transplant thereby leading to potential severe HCV-related liver damage such cirrhosis or fibrosing cholestatic hepatitis.
- Post renal transplant, IFN-containing regimens have been associated with a very low SVR and may induce acute rejection.
- Ribavirin monotherapy, will not induce SVR
- It seems advisable to try and eradicate HCV infection PRIOR to KT, i.e. while the patient is on dialysis therapy.
- After KT, α-IFN plus ribavirin therapy could be attempted only in those patients developing rapid cirrhosis, fibrosing cholestatic hepatitis or *de novo* cryoglobulinemic GN within the allograft
- Hepatoma surveillance essential

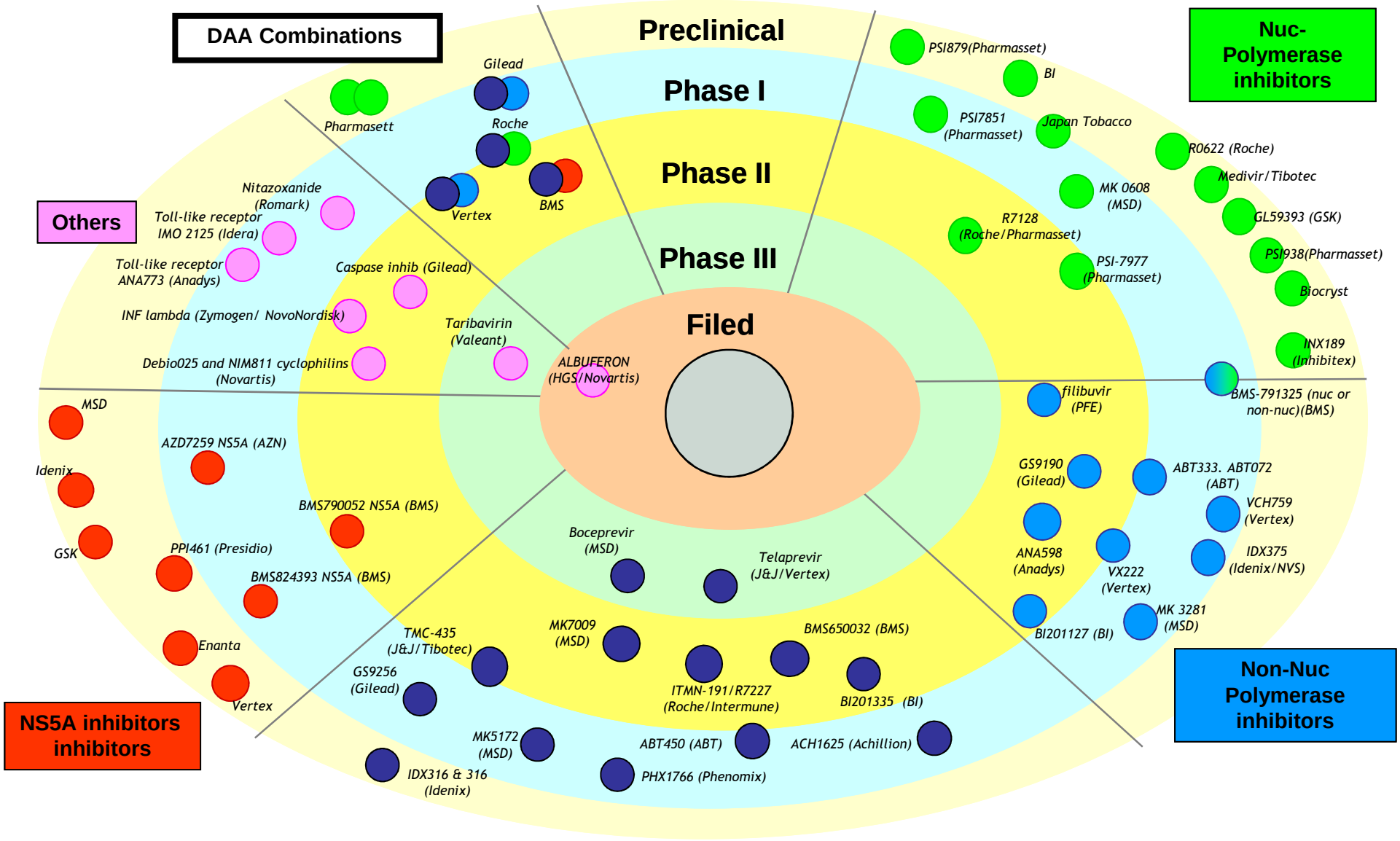
TVR increases serum levels of Immunosuppressants

Calcineurin Inhbitor	C_{max}	AUC	$t_{1/2}$
Cyclosporine A	**1.3-fold increase**	4.6-fold increase	From 12 → 42 hours
Tacrolimus	**9.4-fold increase**	70-fold increase	From 41 → 196 hours

- Telaprevir increases the exposure of drugs metabolised by cytochrome P450-3A4 including immunosuppressants
- Single doses of cyclosporine or tacrolimus had no major effect on telaprevir pharmacokinetics

Garg V, et al. Hepatology 2011; 54: 20-27.

DAA Development Landscape



Looking to the Future

- New drugs may enable us to achieve better SVR rates in renal patients in the near future
- Major obstacles with currently available protease inhibitors will be DDI's and anaemia
- Large-scale, investigator-led studies are needed to fully evaluate the utility of these drugs in the dialysis population
- Interferon-free regimens are now on the horizon. These may offer a real treatment option for post-transplant patients.
- It would appear that ribavirin will still be required in most interferon-free regimens.

Thank You

Figure 1. Right foot lesions before treatment.

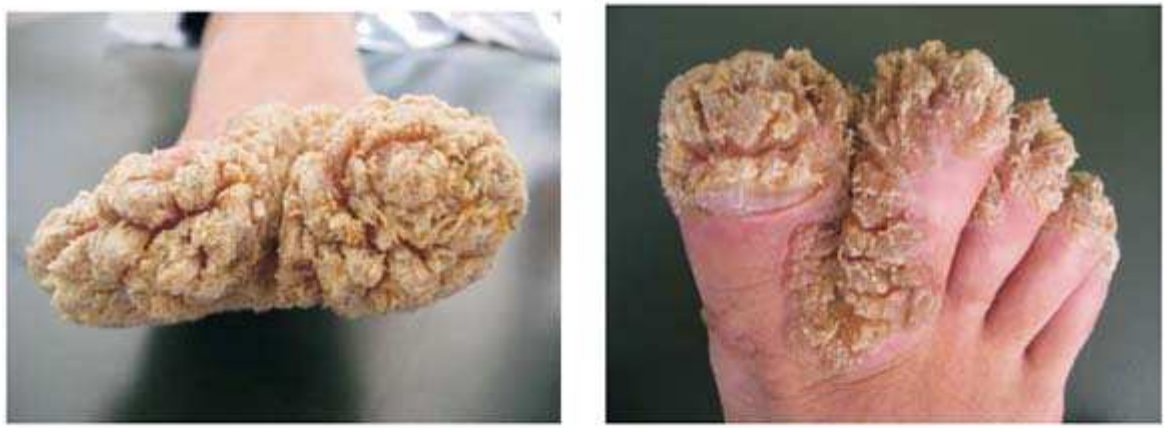


Figure 2. Right foot without lesions seven months after treatment with peg-interferon alfa-2b and ribavirin.