Protease Inhibitors to Treat Hepatitis C in the Swiss HIV Cohort Study: High Efficacy but Low Uptake

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Background & Aims

Hepatitis C Virus (HCV) infection is a major cause of death in HIV infected patients. Until recently, pegylated interferon combined with ribavirin was the standard of care treatment for all HCV genotypes. However, the success of this treatment was limited through low uptake in clinical routine settings, and low efficacy for the most common HCV genotypes. The approval of the HCV protease inhibitors (PIs) telaprevir and boceprevir in 2011 promised higher efficacy in genotype 1 infected patients. However, these first generation directly acting antiviral agents (DAA) have to be combined with pegylated interferon and ribavirin which limits treatment eligibility in many patients. Thus, it was uncertain whether the approval of PIs would have an impact on treatment success at the population level.

The aim of this study was to assess uptake and efficacy of DAAs in a nationwide representative cohort of HIV/HCV-coinfected patients.

Materials and Methods

We evaluated DAA uptake and efficacy in all HIV/HCV genotype 1 coinfected patients in the Swiss HIV Cohort Study (SHCS).

Furthermore, we assessed prospectively DAA efficacy in HIV/HCV-coinfected patients using a standardised case-report form.

Patients who failed treatment were analyzed individually for different risk factors including the emergence of resistance-associated variants.

Results

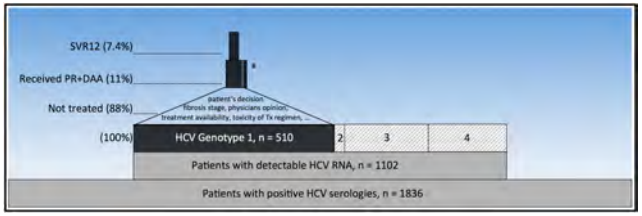
After approval of DAAs in Switzerland in September 2011 to September 2013, 57 SHCS participants started treatment with either Telaprevir, Boceprevir or Faldaprevir (**see Table 1**). Faldaprevir was prescirbed in the frame of an international phase III trial.

Overall, 11% of HIV/HCV coinfected with chronic genotype 1 infection started treatment with DAAs (**Figure 1**).

Virological response rates by DAA and treatment history is shown in **Figure 2**.

Eight patients had virological failure (**Table 2**), 4 patients stopped treatment because of depression and no patient stopped treatment because of somatic toxicities.

Figure 1: Pyramid of Care: Treatment uptake and efficacy in the SHCS



Pyramid of care: Timeframe 09/2011-08/2013, *) 6 Patients received PR without DAA

Table 1: Baseline Characteristics

		treated (n=57)			not treated (n=453)
		Telaprevir (n=37)	Boceprevir (n=8)	Faldaprevir (n=12)	
Age	*median (IQR)*	49 (44-51)	46.5 (44.5-52.5)	41 (35-55)	47 (41-51)
Gender	*males n (%)*	31/37 (84%)	6/8 (75%)	9/12 (82%)	312/453 (69%)
Weight	*kg median (IQR)*	71 (65-79)	58 (56-72)	62.5 (57-70)	68 (58-79)
Liver biopsy/Fibroscan*	≥F3 n (%)	23/33 (70%)	5/7 (71%)	1/11 (9%)	47/217 (22%)
	cirrhotic n (%)	12/33 (36%)	3/7 (43%)	0/11 (0%)	31/217 (14%)
	median days since examination (IQR)	281 (245-737)	347 (206-1744)	355 (245-737)	580 (216-1499)
HCV treatment history	*treatment naïve %*	14/36 (39%)	3/8 (37.5%)	9/12 (75%)	352/453 (78%)
	*previous non-response** %*	19/36 (53%)	2/8 (25%)	0/12 (0%)	101/453 (22%)***
	relapser %	3/36 (8%)	3/8 (37.5%)	3/12 (25%)	n/a***
HCV Genotype	*GT 1A: n (%)*	27/37 (73%)	6/8 (75%)	11/12 (92%)	330/453 (73%)
	GT 1B-E: n (%)	10/37 (27%)	2/8 (25%)	1/12 (8%)	123/453 (27%)
HCV baseline viral load	*log10 median (IQR)*	5.9 (4.3-6.3)	6.3 (5.9-6.7)	6.3 (6.2-6.4)	6.2 (5.7-6.6)
IL28B	*%CC*	12/31 (39%)	3/7 (43%)	4/11 (36%)	n/a
Alcohol intake	*>50g/d: n (%)*	1/36 (3%)	0/7 (0%)	0/11 (0%)	32/162 (32%)
CD4 (baseline)	*cc/mcl, median (IQR)*	569 (444-786)	444 (383-616)	528 (288-654)	539 (380-765)
Suppr. HIV RNA at baseline	*<20 cp/ml: n (%)*	34/37 (92%)	7/8 (88%)	9/11 (82%)	331/453 (73%)
on cART	*n (%)*	37 (100%)	7 (88%)	12 (100%)	387/421 (92%)
cART adherence	*never missed: n (%)*	34/35 (97%)	7/8 (88%)	9/11 (82%)	308/399 (77%)
(baseline, self reported)	*max. 1 missed/month: n (%)*	35/35 (100%)	8/8 (100%)	11/11 (100%)	366/399 (92%)
Mode of HIV transmission	*IDU*	21/37 (57%)	7/8 (88%)	4/11 (36%)	312/453 (69%)
	MSM	5/37 (14%)	1/8 (12%)	4/11 (36%)	43/453 (9%)
	HET	8/37 (22%)	0/8 (0%)	1/11 (9%)	86/453 (19%)
	Others	3/37 (6%)	0/8 (0%)	2/11 (19%)	12/453 (3%)
Ethnicity	*%white*	31/37 (84%)	7/8 (88%)	11/11 (100%)	425/453 (94%)
	%non-white	6/37 (16%)	1/8 (12%)	0/11 (0%)	28/453 (6%)

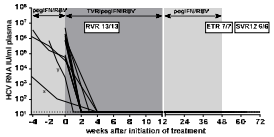
***) Most recent examination:**
- Fibroscan ≥ 9.5 kPa translates to Metavir ≥ F3, Fibroscan ≥ 12.4 kPa translates to cirrhotic

****) previous non-response:** either previous breakthrough, null responder, or partial responder

*****)** not differentiated between previous non-response and relapse in control group of not treated patients

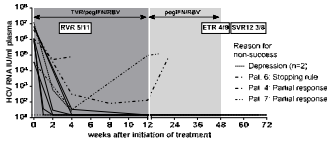
Figure 2: Individual Treatment Response by DAA and treatment history

A. Treatment-naïve/ Telaprevir (n=13)

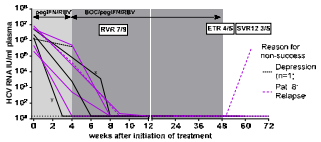


Week 0: Start of standard of care
x: Experimental set-up: Eight weeks lead-in with pegIFN/RBV, weeks -4 to -8 are not shown
y: Two weeks Sebrinin precourse (no pIFN/RBV during that time)
One patient was only treated for 8 weeks with TVR/pegIFN/RBV with a total duration of treatment of 24 weeks

B. Treatment-experienced/ Telaprevir (n=11)

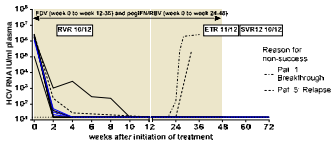


C. Treatment-naïve and Treatment-experienced/ Boceprevir (n=9)



x: Five weeks lead-in, week 5-6 TVR, from week 7 BOC
y: Total treatment length only 28 weeks
purple: treatment experienced

D. Treatment-naïve and prior relapsers/Faldaprevir (n=12)



Blue: prior relapsers

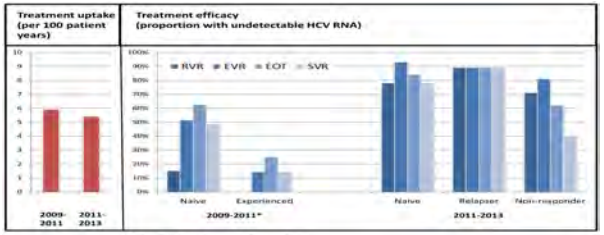
Table 2: Characteristics of patients with virological failures

	Sex	HCV Sub-type	Meta-vir	IL28B	Tx history	Baseline ART	HCV-PI	Tx length (weeks)	Failure reason	Adherence[a]	Substitution	% dose received	Drug resistance mutations at baseline[b]	Drug resistance mutations at failure[b]
Pat. 1	m	1a	F2	CT	naïve	RTV RGV MRV DRV 3TC	FDV	24	breakthrough week 24	≥ 95%	EC, EPO and G-CSF	FDV: 100%, RBV:57.5%, pIFN: 56%	Q80K	Q80K + R155K
Pat. 2	m	1a	F3	CT	null response	TDF RTV RGV ATV	TVR	48	relapse 8 weeks after End of Tx	≥ 95%	EPO	TVR: 100% RBV: 79%, pIFN: 97%	none	R155K
Pat. 3	f	1e	F3	CT	null response	TDF RGV ETC	TVR	48	breakthrough week 36	≥ 95%	G-CSF	TVR: 100% RBV: 68%, pIFN: 67%	none	I132V
Pat. 4	m	1b	F4	TT	experienced (unclear)	TDF RGV ETC	TVR	22	partial response	≥ 95%	EC and EPO	TVR: 100% RBV: 83%, pIFN: 100%	not tested	no sample
Pat. 5	m	1a	F1	TT	naïve	RGV ABC 3TC	FDV	25	relapse 7 weeks after End of Tx	≥ 95%	-	FDV: 100% RBV:100%, pIFN: 83%	none	R155K
Pat. 6	m	1b	F3-4	TT	breakthrough	ETV ABC 3TC	TVR	4	HCV-RNA >1000 at week 4	≥ 95%	-	TVR: 100% RBV: 75%, pIFN: 100%	none	none
Pat. 7	m	1b	F3	CT	breakthrough	TDF RGV ETC	TVR	16	partial response	≥ 95%	-	TVR:100% RBV:100%, pIFN: 100%	not tested	A156S
Pat 8	m	1a	F4	CT	null response	TDF RGV ETC	BOC	48	relapse 14 weeks after End of Tx	≥ 95%	EC, EPO	BOC:100% RBV: 65%, pIFN: 68%	not tested	no sample

[a] Self-reported adherency, % of prescribed drugs that were taken. [b] Drug resistance data are based on population sequencing

Abbreviations: PI: Proteaseinhibitor, Tx: Treatment, EC: erythrocyte concentration, EPO: erythropoietin, BOC: Boceprevir, TVR: Telaprevir, FDV: Faldaprevir, RBV: Ribavirin, pIFN: Peginterferon, RTV: Ritonavir; RGV: Raltegravir; MRV: Maraviroc; DRV: Darunavir; 3TC: Lamivudin; TDF:Tenofovir ; ETC: Emtricitabin; ABC: Abacavir; ETV: Etravirin; ATV: Atazanavir

Figure 3: Uptake and Efficacy before and after approval of DAAs in Switzerland



RVR: Rapid virological response (week 4)
EVR: Early virological response (week 12)
EOT: End of treatment response
SVR: Sustained virological response

Conclusions

Protease-inhibitor based hepatitis C treatment in HIV-infected patients resulted in high virological response rates.

Treatment uptake remained low after the introduction of PIs. Overall, only 11% of patients with chronic HCV genotype 1 infection started therapy. Therefore introduction of PI in clinical routine was beneficial at the individual level, but had only a modest effect on the burden of hepatitis C disease at the population level.

The high efficacy and low rate of toxicity-associated discontinuations suggest an appropriate patient selection and management in clinical routine.

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Aubert V, Barth J, Battegay M, Bernasconi E, Böni J, Bucher HC, Burton-Jeangros C, Calmy A, Cavassini M, Egger M, Elzi L, Fehr J, Fellay J, Furrer H (Chairman of the Clinical and Laboratory Committee), Fux CA, Gorgievski M, Günthard H (President of the SHCS), Haerry D (deputy of "Positive Council"), Hasse B, Hirsch HH, Hösli I, Kahlert C, Kaiser L, Keiser O, Klimkait T, Kouyos R, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Metzner K, Müller N, Nadal D, Pantaleo G, Rauch A (Chairman of the Scientific Board), Regenass S, Rickenbach M (Head of Data Center), Rudin C (Chairman of the Mother & Child Substudy), Schöni-Affolter F, Schmid P, Schultze D, Schüpbach J, Speck R, Staehelin C, Tarr P, Telenti A, Trkola A, Vernazza P, Weber R, Yerly S.