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Excellent outcome of direct antiviral treatment for chronic hepatitis C in Switzerland

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Summary

BACKGROUND: The introduction of direct acting antivirals (DAAs) for the therapy of chronic hepatitis C (CHC) has revolutionised treatment and marks a paradigm shift in the approach to this disease, rendering interferon-based therapies obsolete.

AIMS OF THE STUDY: We retrospectively and prospectively evaluated treatment results after the introduction of DAA in Switzerland in a cohort of patients with CHC.

METHODS: We examined 565 patients who received DAA treatment for CHC between November 2013 and June 2016 with regard to HCV genotype, fibrosis stadium, treatment and outcome. In addition, outcome of re-treatment and resistance-associated substitutions (RAS) in patients that did not achieve sustained virological response (SVR) were evaluated. The majority of patients participate in the Swiss Hepatitis C Cohort Study. Data were evaluated in an intention-to-treat and a modified intention-to-treat analysis.

RESULTS: Overall SVR rate for all patients was 94% (530 of 565, 95% CI 92–96%). Of 350 patients with HCV genotype 1 CHC, 335 achieved SVR, resulting in an SVR rate of 96% (335 of 350, 95% CI 94–98%). Patients with HCV genotype 2 achieved SVR in 94% (48 of 51, 95% CI 87–100%). Patients with HCV genotype 3 showed SVR of 92% (98 of 107, 95% CI 87–97%). In patients with HCV genotype 4, the SVR rate was substantially lower at 85% (49 of 57, 95% CI 76–94%). The rate of advanced liver fibrosis (Metavir F3/F4) assessed by means of liver biopsy or Fibroscan® in the entire patient population was 71% (404 of 565). Out of 35 patients that did not achieve SVR after DAA treatment, 32 had a relapse and 3 patients showed viral breakthrough. In 17 of 35 cases (49%) patients were treatment naïve and 21 of 35 patients (60%) were cirrhotic. RAS genotyping of HCV was performed in 14 patients. Nine of these 14 patients (60%) carried muta-

tions in the NS5A region of the virus genome. Twenty-seven percent of patients who experienced treatment failure were not treated with recommended regimens as a result of drug availability and reimbursement limitations.

CONCLUSION: In Switzerland, novel DAA treatments for CHC reflect the positive results from registration trials. Genotypes 2 and 4 remained more difficult to treat between 2014 and 2016. Patients who experienced a relapse after DAA treatment in Switzerland predominantly showed mutations in the NS5A region of the virus genome. DAA treatment limitations in Switzerland did prevent optimal treatment regimens in some patients.

Key words: chronic Hepatitis C, direct acting antivirals, sustained virological response

Introduction

Interferon-free direct antiviral agents (DAAs) for the treatment of chronic hepatitis C (CHC) became available in Switzerland in December 2013. In large registration studies, DAA treatment resulted in sustained virological response (SVR) rates of more than 90% in many patient populations with minimal side effects [1–3]. Based on these registration studies, recommendations of the major national and international societies quickly adopted the novel treatment regimens for most patients, rendering previous pegylated-interferon (PEG-IFN)-based regimens obsolete (summarised in the EASL and AASLD guidelines on the

ABBREVIATIONS	
CHC	chronic hepatitis C
DAA	direct acting antivirals
EASL	European Association for the Study of the Liver
HBV	hepatitis B virus
HCV	hepatitis C virus
ITT	intention to treat
PEG-IFN	pegylated interferon
RAS	resistance associated substitutions
SVR	sustained virological response

treatment of chronic hepatitis C virus [HCV] infection) [4, 5].

With the widespread use of DAA in diverse clinical settings and patient populations, initial registration study results have been challenged by so-called "real life" data that, in several cases, were clearly inferior to the SVR rates expected on the basis of phase III trials [6, 7]. These data remain controversial, with other studies finding SVR rates similar to registration trials (e.g., treatment in age >65 [8] or human immunodeficiency virus [HIV] co-infected [9]). Given the significant cost and burden to healthcare systems due to the high large number of CHC patients and the high costs of DAA, the success rate and performance of these novel drugs in a clinical situation outside of registration studies is of major interest. Furthermore, it allows for the evaluation of recommended treatment regimens as well as critical evaluation of current local access to medication and reimbursement restrictions.

The aim of this study was to assess treatment regimens and success rates of patients with CHC in Switzerland, and to review access and reimbursement limitations with regards to treatment outcome.

Materials and methods

Study design
This was an observational study assessing treatment regimens and treatment outcome of a patient cohort suffering from CHC. Reporting of data follows the STROBE Statement (Strengthening the Reporting of Observational studies in Epidemiology) for observational epidemiological studies [10].

Setting
The present study was conducted at three Swiss tertiary care centres (University Hospital Zurich, Kantonsspital St Gallen, Epatocentro Ticino, Lugano). Data collection was performed retrospectively as well as prospectively. Data were analysed per intention-to-treat (ITT) analysis, and per modified ITT analysis with respect to HCV genotype, regimen of DAA therapy, treatment outcome as well as retreatment in patients who did not achieve SVR after the first course of DAA. Patients were recruited between November 2013 and June 2016. Most patients are participants in the Swiss Hepatitis C Cohort Study [11].

Participants
Five hundred and eighty-five patients with CHC undergoing DAA treatment between November 2013 and June 2016 were evaluated. DAA treatment regimens were chosen according to current recommendations of the European Association for the study of the Liver (EASL), Swiss expert opinion statement and/or treatment according to availability, and reimbursement limitations of the Swiss health authorities.

Inclusion criteria were (1) age older than 18 years (2), a documented HCV infection (3), a DAA-based therapy for CHC (4), available data on HCV treatment including laboratory data and documented HCV viral load (HCV RNA by PCR [COBAS 4800; Roche Diagnostics, Rotkreuz, Schweiz]), and (5) patient informed consent. Patients not meeting these criteria were not included in the study (see

fig. 1). Concomitant liver diseases and co-infections were recorded if available.

Variables
Patients were divided into five groups according to HCV genotype and subtype (1a, 1b, 2–4). Patients with HCV genotype 1 were divided into the subgroups 1a and 1b, since the treatment regimen differs for the two subtypes. In contrast, the other HCV genotypes (2, 3 and 4) were treated with a genotype-specific regimen regardless of subtype. Because of the scarcity of these genotypes in Switzerland, no patients with HCV genotype 5 or 6 infection were included in the study. Successful treatment was defined as negative HCV-PCR 12 weeks after end of treatment (SVR12). Treatment failure was defined as again positive HCV-PCR during antiviral therapy (breakthrough) or after end of treatment (relapse).

Data sources/measurement
HCV genotyping was performed by a line probe assay (Versant HCV Genotype 2.0 Assay, Siemens/Realtime HCV Genotype II, Abbott) and assessment of viral load was performed by a PCR-based test (COBAS 4800; Roche Diagnostics, Rotkreuz, Schweiz). SVR was defined as undetectable HCV RNA by PCR at week 12 after treatment. The lower limit of detection of the HCV-PCR assay was 10 IU/ml at University Hospital Zurich and 15 IU/ml at Kantosspital St Gallen and Epatocentro Ticino. Liver fibrosis was assessed histologically by means of liver biopsy or non-invasively by transient elastography (Fibroscan®). Results were graded according to Metavir F stages with transient elastography values of >9.5 kPa corresponding to Metavir F3 while transient elastography values >12.5 equalling Metavir F4 [12]. If both biopsy and transient elastography results were available, transient elastography values were only used for analysis if more recent than biopsy.

Bias
To control for a selection bias, the study had defined inclusion and exclusion criteria, which reflects the Swiss CHC population undergoing antiviral treatment.

Study size
All patients with CHC undergoing DAA treatment between November 2013 and June 2016 from three tertiary Swiss hepatology centres were screened for study participation.

Statistical methods
Statistical analysis was performed using SPSS 22.0 (IBM Corp, Armonk, NY USA). Graphs were generated using PowerPoint (Version 14.6.9, Microsoft PowerPoint Mac OS X 2011). Patients lost to follow-up were excluded before performing statistical evaluations (see fig. 1).

Ethics statement
The study protocol was designed according to the ethical guidelines of the 1975 Helsinki Declaration. The ethics committee of the Canton of Zurich (BASEC 2016-00341) and the ethics committees of the participating centres (BASEC 2016-00171) approved the present study. Written

informed consent of all patients was obtained. For the statistical analysis all clinical data were anonymised.

Results

Patient and treatment characteristics

A total of 584 patients from three centres undergoing DAA treatment for CHC were evaluated. Eighteen patients did not meet inclusion criteria and were therefore excluded from further analysis (fig. 1). The 565 remaining patients that underwent DAA treatment with a minimal post-treatment follow-up of 12 weeks were included and a modified ITT analysis was performed. Characteristics of the cohort are shown in table 1. Seventy-one percent (403 of 565, 71.3%) of patients had Metavir F3 or F4 fibrosis as determined by biopsy or transient elastography. Two hundred and fifty-seven patients in our study suffered from liver cirrhosis (liver fibrosis stage F4). Among those cirrhotic patients there were 197 patients with Child-Pugh Class A (197 of 257, 77%) and 18 patients with Child-Pugh Class B (18 of 257, 7%). There was no cirrhotic patient with Child-Pugh Class C. Five-hundred-twelve patients received an interferon-free DAA combination ± ribavirin (512 of 565, 90.6%) and 53 patients a combination of PEG-IFN, ribavirin and sofosbuvir (53 of 565, 9.4%). Mean treatment duration for all patients was 15 weeks. Overall SVR rate was 94% (530 of 565, 93.8%, 95% CI 92–96%) for all patients treated (fig. 2). Of the patients without cirrhosis (fibrosis stage F1–F3), 95% reached SVR (286 of 300, 95% CI 93–97%). SVR rate in patients with liver cirrhosis (fibrosis stage F4) was lower (236 of 259, 92%, 95% CI 88–94%). Cirrhotic patients with Child-Pugh Class A reached SVR in 91% (179 of 197, 95% CI 87–95%) and cirrhotic patients with Child-Pugh Class B reached SVR in 83% (15 of 18, 95% CI 65–100%]) of cases. Fifty-five percent of all patients were treatment naïve (310 of 565, 54.9%), 46 patients had a concomitant HIV infection (46 of 565, 8.1%), 6 patients had a hepatitis B virus (HBV) infection (6 of 565, 1%) and 2 patients suffered from HIV and HBV co-infection (2 of 565, 0.4%). There was one case of each of the following: primary biliary cholangitis, primary sclerosing cholangitis, haemochromatosis, autoimmune hepatitis and Wilson's disease (1 of 565, 0.2%). Reasons for exclusion from the final analysis were liver transplantation during the course of therapy (5 of 584,

0.9%), change in HCV treatment (2 of 584, 0.3%) and missing data (2 of 584, 0.3%). One patient stopped the treatment because of reasons other than adverse events (1 of 584, 0.2%). There were no SVR data for five patients at the time of analysis (5 of 584, 0.9%) and four patients (4 of 584, 0.7%) were lost to follow-up.

Reporting SVR results by ITT analysis, overall SVR rates were (530 of 575, 92%, 95% CI 90–94%). In this analysis the following 10 patients are included: one patient who stopped the treatment (1 of 10, 10%), five patients who had no SVR value (5 of 10, 50%) and four patients who were lost to follow-up (4 of 10, 40%). The following results on treatment outcome are from a modified ITT from which the previously mentioned 10 patients were excluded.

Figure 1: Flow chart of patient recruitment.

Table 1: Patients' baseline characteristics (n = 565).

Age (years), median (range)	56 (21–86)
Male sex, n (%)	356 (63.0)
Body mass index (kg/m^2), mean (range)]	25.34 (16.0–41.9)
HCV genotype, n (%)	
1	350 (62.0)
2	51 (9.0)
3	107 (18.9)
4	57 (10.1)
HCV RNA (log^{10} IU/ml), median (range)	6.08 (1.5–7.5)
Liver stiffness (kPa), median (range)	12.10 (3.1–75.0)
Treatment history, n (%)	
Treatment naive	310 (54.9)
Relapse	128 (22.7)
Breakthrough	19 (3.4)
Non-response	85 (15.0)
Premature discontinuation	21 (3.7)
Other	2 (0.4)
Co-infections, n (%)	
HIV	46 (8.1)
HBV	6 (1.1)
HIV + HBV	2 (0.4)
No co-infection	511 (90.4)
Metavir, n (%)	
F1 (≤7.5)	78 (13.8)
F2 (7.6–9.5)	76 (13.5)
F3 (9.6–12.5)	146 (25.8)
F4 (≥12.6)	257 (45.5)
No data	8 (1.4)

HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus
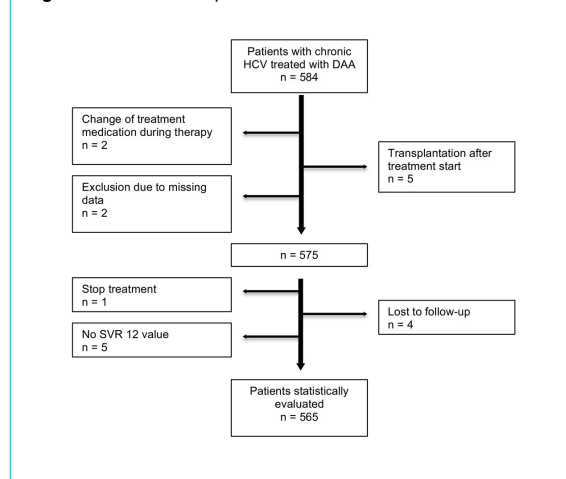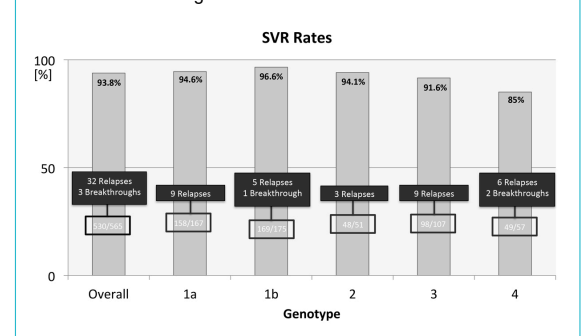

Figure 2: Overall SVR rate and SVR rates for individual HCV genotypes. Eight patients with not further specified genotype 1 are not included in this figure.

Treatment outcome by genotype

Patients with HCV genotype 1a (n = 167; supplementary fig. S1a in appendix 1) had an overall SVR rate of 95% (158 of 167, 95% CI 92–98%). Seventy-one percent (118 of 167) of patients with genotype 1a had advanced fibrosis (Metavir F3/4), and 94% (111 of 118, 95% CI 90–98%) of these achieved SVR. Genotype 1a patients received sofosbuvir-containing treatment in 81% (136 of 167), while 19% (31 of 167) were treated with a combination of ritonavir-boosted paritaprevir with ombitasvir and dasabuvir with (n = 26) or without (n = 5) ribavirin for 12 weeks. In the patient group that received paritaprevir/ritonavir/ombitasvir and dasabuvir, 3 out of 31 patients (9.6%) did not reach SVR. Sofosbuvir was most frequently combined with ledipasvir (95 of 136 sofosbuvir treatments, 70%), daclatasvir (13 of 135 sofosbuvir treatments, 9.5%) and simeprevir (11 of 136 sofosbuvir treatments, 8%). Seventeen patients were treated with sofosbuvir and ribavirin only (17 of 136 sofosbuvir treatments, 12.5%). Overall SVR rate of sofosbuvir-containing regimens was 95% (130 of 136, 95% CI 91–99%). Most relapses (5 out of 95, 5%) were seen in patients receiving a combination of sofosbuvir/ledipasvir with or without ribavirin for 8 weeks (one relapse without ribavirin; see fig. 3), 12 weeks (three relapses) or 24 weeks (one relapse). All patients who received sofosbuvir/ribavirin for 12 or 24 weeks (n = 17) or sofosbuvir/daclatasvir with or without ribavirin for 24 weeks (n = 13) reached SVR, while there was one relapse among the 11 patients treated with sofosbuvir/simeprevir/ribavirin for 12 weeks (1 of 11, 9%). Of all relapses, most patients were cirrhotic and/or had prior treatment failure (7 of 9, 78%).

Genotype 1b patients (fig. S1b) were treated with sofosbuvir-containing regimens in 69% (120 of 175). Most of these patients had a combination of sofosbuvir with ledipasvir with or without ribavirin (89 of 120, 74%). Twelve patients had a combination of sofosbuvir plus ribavirin (12 of 120, 10%), 8 patients received sofosbuvir plus daclatasvir with or without ribavirin (8 of 120, 7%) and 11 patients were treated with sofosbuvir plus simeprevir with or without ribavirin (11 of 120, 9%). Fifty-four patients were treated with paritaprevir/ritonavir/ombitasvir and dasabuvir with or without ribavirin in 31% of cases (54 of 175). One patient received a combination of daclatasvir/simeprevir for 12 weeks but did have a viral breakthrough. All other genotype 1b relapses occurred in patients treated with sofosbuvir containing regimens (5 of 120; 4%), while all patients that received paritaprevir/ritonavir/ombitasvir and dasabuvir with or without ribavirin for 12 weeks or 24 weeks reached SVR.

For genotype 2 HCV patients (fig. S2), the only DAA regimen available in Switzerland until 2016 was sofosbuvir/ribavirin for 12, 16, 20 or 24 weeks. Thirty-six were treated for 12 weeks, 5 for 16 weeks, 7 for 20 weeks and 3 for 24 weeks. Three out of 51 patients (6%) did not achieve SVR. One patient was a treatment-naïve cirrhotic and received sofosbuvir/ribavirin for 12 weeks, the other two patients were treatment-experienced. One of them was cirrhotic and was treated for 20 weeks.

Similarly, all 107 genotype 3 patients (fig. S3) received a sofosbuvir-based treatment. For most patients sofosbuvir, was combined with daclatasvir with or without ribavirin for 12 or 24 weeks (52 of 107; 49%) or sofosbuvir was given with ribavirin for 12, 24 or 36 weeks (50 of 107; 47%).

Relapse rate in the sofosbuvir/ribavirin group was 6% (3 of 50, 6%), with one relapse after 12 weeks and two after 24 weeks of therapy. Four patients were treated with sofosbuvir/ledipasvir and one of these (25%) experienced a relapse. One patient received a combination with sofosbuvir and simeprevir without ribavirin for 12 weeks and did achieve SVR.

The majority of genotype 4 patients (fig. S4) also received sofosbuvir as part of the DAA treatment regimen (52 out of 57; 91%). The majority received sofosbuvir in combination with ribavirin (22 out of 52, 42%), followed by sofosbuvir/ledipasvir (20 out of 52, 38%). Seven patients were treated with a sofosbuvir/simeprevir regimen with ribavirin (5 of 7, 71%) for 12 weeks or without ribavirin (1 of 7, 14%) for 24 weeks. One patient (1 of 7, 14%) was treated with sofosbuvir/simeprevir for 12 weeks without ribavirin and still reached SVR. Three patients received sofosbuvir/daclatasvir with (1 out of 3, 33%) or without ribavirin (2 out of 3, 67%) for 24 weeks. The remaining 9% (5 out of 57, 9%) were treated with paritaprevir/ritonavir/ombitasvir and ribavirin for 12 weeks.

Of all HCV genotypes, patients with genotype 4 had the largest number of relapses (8 out of 57; 14%). Of all genotype 4 patients 56% (32 out of 57) were treatment-experienced and 53% (30 out of 57) were cirrhotic. Genotype 4 without SVR were treatment-experienced in 63% (5 of 8) and cirrhotic in 63% (5 of 8) of cases. Most relapses occurred in the group that received sofosbuvir/ribavirin for 24 weeks, with 5 (5 out of 22, 23%) patients relapsing and one (1 out of 22, 5%) showing a breakthrough during therapy. In contrast, all patients that received sofosbuvir/ledipasvir (± ribavirin for 12 or 24 weeks) (20 of 20, 100%) and all three that received sofosbuvir/daclatasvir (± ribavirin for 24 weeks) reached SVR. Of 5 patients who received paritaprevir/ritonavir/ombitasvir with ribavirin for 12 weeks, 4 patients achieved SVR (4 out of 5, 80%) with 1 breakthrough.

Overall, 53 patients received their DAA treatment in combination with PEG-IFN. Sixteen patients (16 out of 167; 10%) with genotype 1a received a sofosbuvir/ribavirin therapy with PEG-IFN for 12 weeks (15 out of 16) or 24 weeks (1 out of 16). All of them reached SVR. In the genotype 1b group only 11 patients (11 out of 175; 6%) received a sofosbuvir/ribavirin/PEG-IFN combination for 12 weeks. Two of them did not reach SVR (2 out of 11). Of all genotypes, genotype 3 had the largest number of patients treated with PEG-IFN (20 out of 107; 19%). Ten patients received a sofosbuvir/ribavirin/PEG-IFN combination for 12 or 24 weeks, and 10 received a sofosbuvir/daclatasvir/PEG-IFN combination with or without ribavirin. Two (10%) of the genotype 3 patients that received DAA plus PEG-IFN did not achieve SVR. Six patients in the genotype 4 group also received a combination with sofosbuvir/ribavirin and PEG-IFN for 12 weeks (6 of 57; 11%) and they all reached SVR.

As shown in figure 2, 35 patients in total did not achieve an SVR (32 relapses, 3 breakthroughs). If a relapse occurred, it usually became apparent within the first four weeks of the end of treatment. Later relapses were only seen in 3 out of 35 cases. Patients who did relapse had advanced fibrosis in 89% (31 out of 35) versus 68% in the group of patients that did achieve SVR (358 out of 530). Of all 35 patients who experienced treatment failure, 17 were treat-

ment-naïve (49%). Of all 530 patients who reached SVR, 293 were treatment naïve (293 out of 530, 55%).

Resistance-associated substitutions (RAS) were analysed in 14 out of 35 (40%) treatment failure patients. The most frequent RAS occurred in the NS5A gene (9 out of 14; 60%). This is in concordance with international studies on RAS incidence [13–15]

Re-treatment of this group was successful in a large proportion of patients (fig. 3). Of 16 patients that did receive re-treatment, 14 patients achieved SVR (88%). For several patients, reimbursement of re-treatment is currently under revision. Only one patient did not have any further treatment options based on his RAS profile.

Discussion

This Swiss data for novel DAA treatment of CHC shows SVR rates very similar to those from the registration trials [1–3, 16]. This is in accordance with other studies that also reproduce the generally excellent SVR rates, especially among patients with genotype 1 CHC [17–19]. For the observed time period between 2014 and mid-2016, genotypes 2 and especially 4 had limited treatment options. The data reported here do not take into account the introduction of novel DAAs such as elbasvir/grazoprevir (April 2016) and sofosbuvir/velpatasvir (January 2017) that were licensed after this study and should significantly improve the SVR rates in these patient groups [20, 21]

Most relapses were detected early in the post-treatment period, usually within the first 4 weeks. Fortunately, re-treatment was successful in most patients.

Access to DAA treatment and reimbursement of the very high therapy costs is a worldwide challenge for HCV patients as well as for healthcare systems [22–25]. Limitations of access and reimbursement have been introduced in many countries [26]. Beginning in 2014, the reimbursement of DAA therapies in Switzerland was limited to patients that had histologically verified advanced fibrosis or cirrhosis (Metavir F3 or F4) or showed transient elastography values >9.5 kPa in two consecutive measurements with a minimum interval of 3 months [27]. Moreover, several of the recommended therapeutics were not approved or reimbursed. This made modifications and deviations from the treatment recommendations by EASL necessary in 2014 and early 2015. Thirty percent of patients that did suffer a relapse were not treated according to international guidelines due to limitations of availability or reimbursement. Until the market introduction of paritaprevir/ritonavir/ombitasvir plus ribavirin, and grazoprevir/elbasvir in mid-2016, there was no approved interferon-free treatment regimen for HCV genotype 4 available in Switzerland, and alternative treatments required case-by-case approval of reimbursement by health insurance providers.

Since the analysis of our data, several pan-genotypic treatments have been approved that show high efficacy and SVR rates. Moreover, limitation for treatment reimbursement according to fibrosis grade has been lifted mean-

Figure 3: Treatment and re-treatment of relapsing patients and clinically relevant RAS.DCV = daclatasvir; DSV = dasabuvir; ETR = end-of-treatment response; GT = genotype; HIV = human immunodeficiency virus; LDV = ledipasvir; n.a. = test results not available or no RAS test was performed; n/t = not taken (patient did not take RBV); PAR = paritaprevir; OMB = ombitasvir; PEG-INF = pegylated interferon; RAS = resistance associated substitutions; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SVR = sustained virological response; SVR12 = negative HCV-PCR 12 weeks after end of treatment; SVR24 = negative HCV-PCR 12 weeks after end of treatment.* No RAS detected.

Failed treatment	Age	Sex	Metavir	Coinfection	GT	Treatment History	Baseline viral load	NS5B	NS5A	NS3	PEG-INF	RBV	Duration (Week)	Outcome	yes=1/no=0	NS5B	NS5A	NS3	Date	NS5B	NS5A	NS3	Ribavirin	Duration	Outcome
SOF/RBV or SOF/RBV/PEG-INF	59	m	4	NO	1b	Treatment naive	530'000	SOF			YES	YES	12	Relapse	NO				06.05.15	SOF	LDV		YES	24	SVR12
	63	f	4	NO	1b	Relapse	5'900'000	SOF			YES	YES	12	Relapse	n.a.				04.03.16	SOF	LDV		YES	12	SVR12
	55	m	3	NO	2	Treatment naive	6'000'000	SOF			NO	YES	12	Relapse	YES		T58P		11.09.15	SOF			YES	24	SVR12
	75	f	2	NO	2	Relapse	1'411'478	SOF			NO	YES	12	Relapse	YES		R30K		no data						
	63	f	2	NO	2	Null-response	475727	SOF			NO	YES	20	Relapse	n.a.				no data						
	60	m	4	NO	3	Null-response	10'000'000	SOF			YES	YES	12	Relapse	n.a.				29.03.16	SOF	DCV	NO	12	SVR12	
	54	m	4	NO	3	Treatment naive	3'400'000	SOF			NO	YES	24	Relapse	n.a.				13.08.15	SOF	LDV	YES	24	SVR12	
	56	m	4	NO	3	Partial non-response	820'000	SOF			NO	YES	24	Relapse	n.a.				07.09.15	SOF	DCV	YES	24	Relapse	
	56	f	3	HIV	3	Treatment naive	5'166'240	SOF			NO	YES	24	Relapse	YES		Q30K		02.02.16	SOF	DCV	YES	24	SVR12	
	64	m	4	NO	3	Breakthrough	1'677'893	SOF			NO	YES	24	Relapse	YES		no		no data						
	49	f	4	NO	4	Treatment naive	4'000'000	SOF			NO	YES	24	Relapse	NO				26.10.16	SOF	DCV	YES	24	SVR12	
	50	m	4	NO	4	Treatment naive	320'000	SOF			NO	YES	24	Relapse	NO				04.01.16	SOF	LDV	YES	8	SVR12	
	61	m	4	NO	4	Partial non-response	2'300'000	SOF			NO	YES	24	Relapse	n.a.				29.02.16	DSV	OMB	PAR	YES	24	Breakthrough
	59	f	3	NO	4	Treatment naive	6'900'000	SOF			NO	YES	24	Breakthrough	n.a.				no therapy						
	57	f	1	NO	4	Relapse	820'000	SOF			NO	YES	24	Relapse	n.a.				18.08.15	DSV	OMB	PAR	YES	12	SVR12
	64	m	3	NO	4	Null-response	940'000	SOF			NO	YES	24	Relapse	n.a.				03.11.15	SOF	SOF	YES	24	SVR12	
SOF/SMV	54	m	4	NO	1a	Null-response	882754	SOF		SMV	NO	YES	12	Relapse	n.a.				no data						
	46	m	4	NO	1a	Null-response	200'000	SOF		SMV	NO	YES	12	Relapse	n.a.				10.06.16	SOF	LDV	YES	24	ETR	
NS5A inhibitor containing regimen	57	m	1	NO	1a	Treatment naive	3'000'000	SOF	LDV		NO	NO	8	Relapse	NO				24.05.16	SOF	DCV		12	SVR12	
	48	m	4	HIV	1a	Treatment naive	367'718	SOF	LDV		NO	YES	12	Relapse	YES		A92E Y93H		no therapy						
	74	m	3	NO	1b	Null-response	11'700'000	SOF	LDV		NO	NO	12	Relapse	YES		A92E Y93H		no data						
	46	m	4	NO	1a	Treatment naive	3'962'801	DSV	OMB	PAR	NO	n/t	12	Relapse	YES			R155K T54S Q80K	no data						
	63	m	3	NO	1a	Treatment naive	21'486'124	DSV	OMB	PAR	NO	n/t	12	Relapse	n.a.				no data						
	44	m	4	NO	1a	Treatment naive	2990760	DSV	OMB	PAR	NO	YES	12	Relapse	n.a.				no data						
	52	m	2	NO	1a	Breakthrough	5'900'000	SOF	LDV		NO	NO	12	Relapse	YES		Q30H Y93H	Q80K							
	50	f	3	NO	1a	Treatment naive	n	SOF	LDV		NO	NO	12	Relapse	NO										
	57	m	3	NO	1b	Treatment naive	100'000	SOF	LDV		NO	NO	12	Relapse	YES		L31M Y93H		20.09.16	SOF	SMV	YES	12	ETR	
	53	f	3	NO	1b	Treatment naive	990'000		DCV	SMV	NO	NO	12	Breakthrough	YES			D168A	no therapy						
	63	m	4	NO	1a	Null-response	3'500'000	SOF	LDV		NO	NO	24	Relapse	YES		Q30R L31M		no therapy						
	64	m	4	NO	1b	Null-response	3'100'000	SOF	LDV		NO	NO	24	Relapse	YES	C316N	Y93H		no therapy						
	56	m	4	NO	3	Partial non-response	3'800'000	SOF	LDV		NO	NO	12	Relapse	NO				31.05.16	SOF	DCV	YES	24	ETR	
	50	m	3	NO	3	Treatment naive	3'500'000	SOF	DCV		NO	YES	12	Relapse	n.a.				no therapy						
	56	m	4	NO	3	Relapse	240'000	SOF	DCV		NO	YES	24	Relapse	YES		A30K		no therapy						
	57	f	4	NO	3	Treatment naive	1'727'635	SOF			NO	YES	24	Relapse	n.a.				no data						
	61	m	4	NO	4	Relapse	n		OMB	PAR	NO	YES	12	Breakthrough	n.a.				no therapy						

while. These new circumstances expand the population of HCV patients that will be treated. Future studies will need to include data on these new patient populations and medications.

This study highlights the importance of the early adoption of internationally accepted treatment guidelines, if possible. Moreover, approved but suboptimal treatment regimens that did comply with national drug availability and reimbursement limitations may have generated excessive costs for the healthcare system.

Our study has limitations. Patients were only included from three referral centres in this non-randomised observational study with a retro- and prospective follow-up. Therefore, the study population might not reflect the standard Swiss HCV population. But at the same time, patients with advanced fibrosis and cirrhosis might be overrepresented in this tertiary care population. As we have shown, the SVR rate in this population is lower, and therefore these excellent SVR results might nevertheless be representative for Switzerland. Finally, the median follow-up period is relatively short, but it is well documented that late relapses are extremely uncommon [28]. Accordingly, this short follow-up has no relevant impact on the SVR reported in this study

In summary, data from Switzerland for DAA treatment in CHC confirm the excellent efficacy of these drugs. These results are novel and have not been reported for Switzerland so far. They are in line with other national and international studies reporting excellent overall outcomes for DAA in a post-approval real-life setting. Patients who do suffer a relapse can in most cases be successfully re-treated. Limitations of access prevented optimal therapy in some patients.

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Appendix 1

Supplementary data

Explanation of supplementary figures

Patients with relapse or breakthrough are marked in orange. Patients marked in yellow received PEG-IFN in addition to their DAA therapy. The number of patients receiving PEG-IFN is marked with *.

16 patients with genotype 1a and 11 patients with genotype 1b were treated with DAA plus PEG-IFN. None of the patients with genotype 2 were treated with additional PEG-IFN. Twenty patients with genotype 3 and 6 patients with genotype 4 were treated with DAA plus PEG-IFN. Eight patients with HCV genotype 1 were excluded from analysis becaue of lack of HCV subtyping.

NON = no second DAA; n/t = not taken (patient did not take RBV); GT = genotype; BT = breakthrough; DCV = daclatasvir; DSV = dasabuvir; GT = genotype; LDV = ledipasvir; PTV/r/OBV = paritaprevir/ritonavir/ombitasvir; RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; PEG-IFN = pegylated interferon.

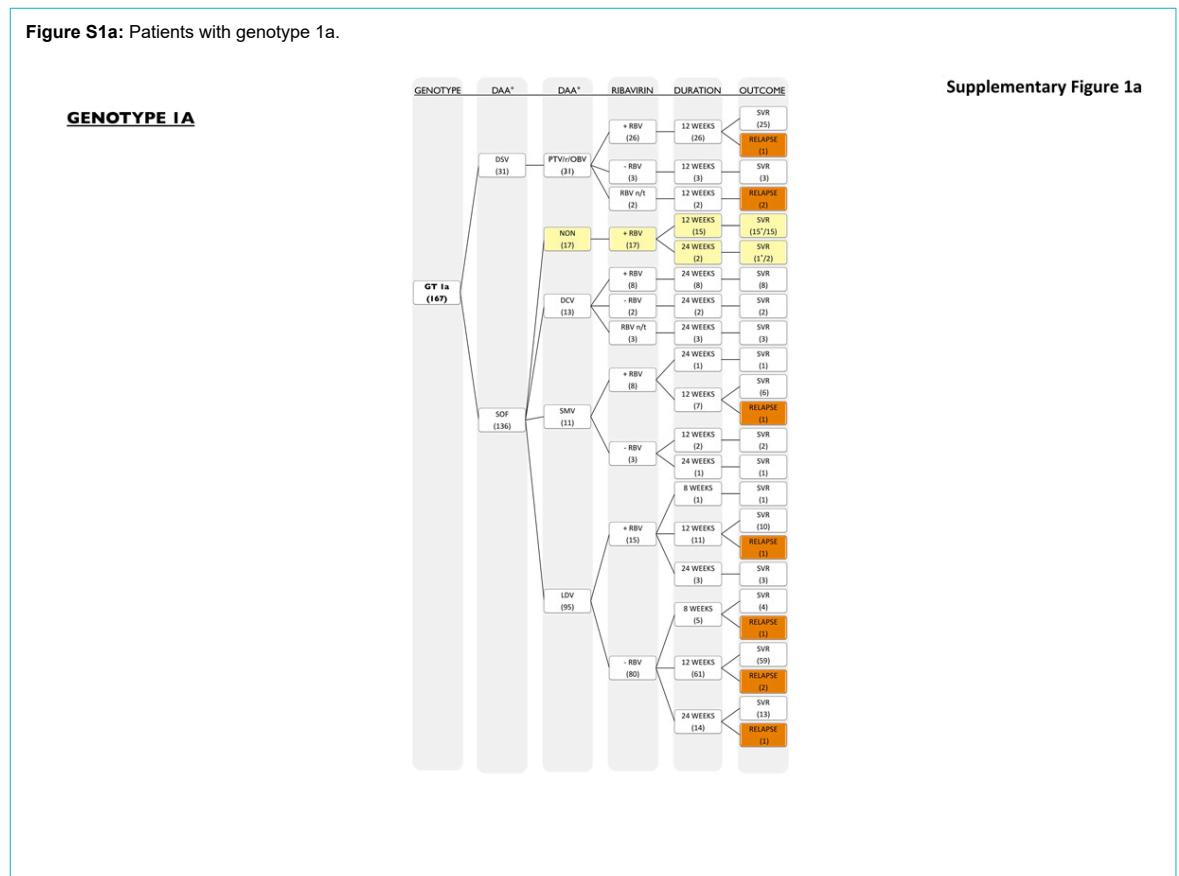### Supplementary figures

Figure S1a: Patients with genotype 1a.

Figure S1b: Patients with genotype 1b.
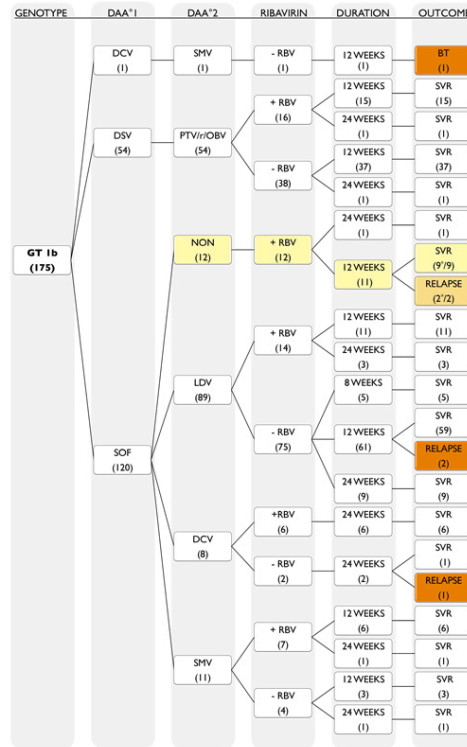
Supplementary Figure 1b

Figure S2: Patients with genotype 2.

Supplementary Figure 2

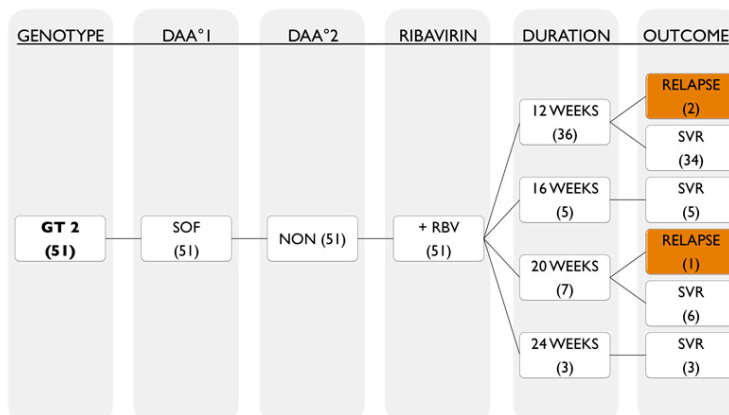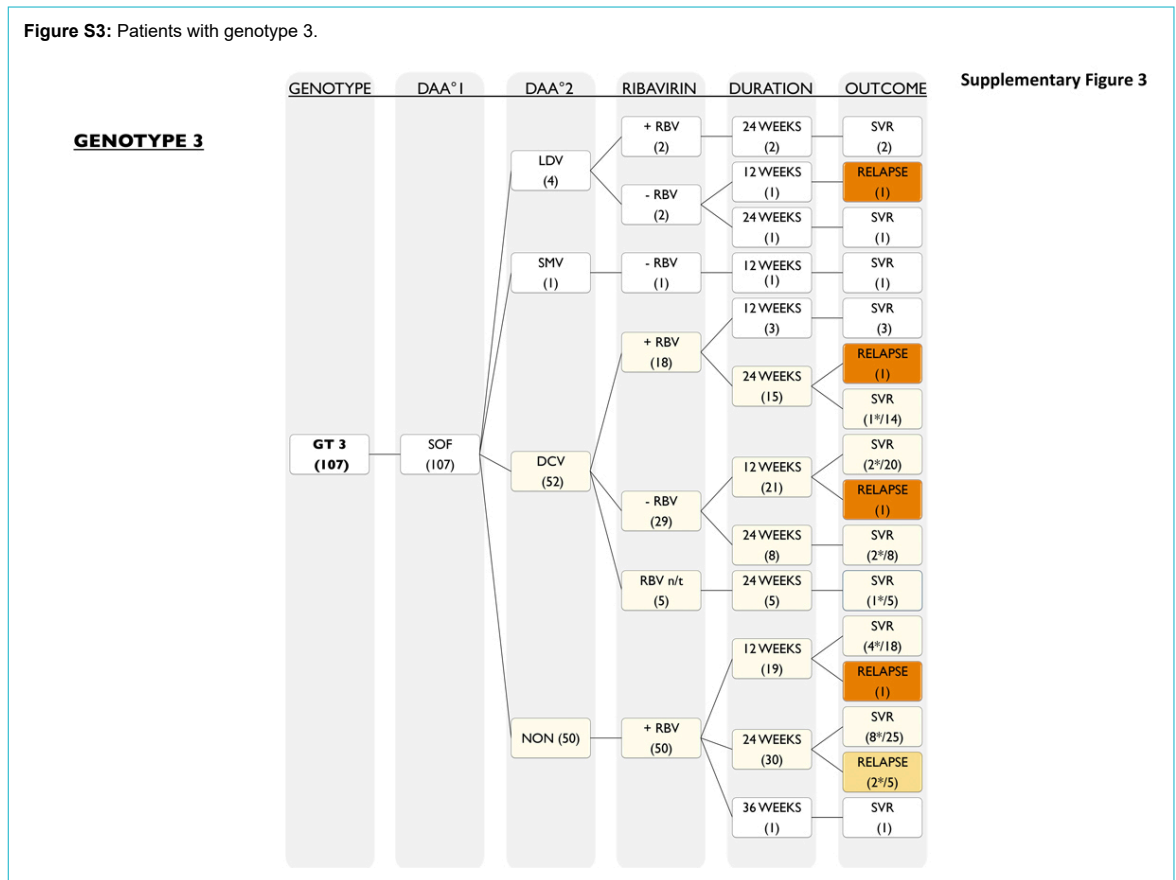**Figure S3:** Patients with genotype 3.

Supplementary Figure 3

Figure S4: Patients with genotype 4.

Supplementary Figure 4