DIRECTLY OBSERVED THERAPY OF CHRONIC HEPATITIS C WITH INTERFERON-FREE ALL-ORAL REGIMENS AT A LOW-THRESHOLD DRUG TREATMENT FACILITY – A NEW CONCEPT FOR TREATMENT OF PATIENTS WITH BORDERLINE COMPLIANCE RECEIVING OPIOID AGONIST THERAPY

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BACKGROUND

Prevalence of chronic hepatitis C is high in people who inject drugs (PWID). An important subgroup of PWID is defined by the following characteristics: Patients receive Opioid Agonist Therapy under direct observation of a physician or nurse at a low-threshold facility or pharmacy at a daily basis. Most of them suffer from psychiatric comorbidities and thus have contraindications against interferon-based antiviral treatment. They have a borderline compliance and hence are reluctant to go to specialized hepatitis centers. In contrast, their compliance is excellent with respect to their daily visits at the low-threshold facility or pharmacy for ingestion of their opioid substitution therapy. Our hypothesis was that chronic hepatitis C in these patients could perfectly be treated if modern, interferon-free all-oral regimens were applied together with Opioid Agonist Therapy under direct observation of a physician or nurse at a low-threshold facility. In this paper we report our observation that adherence to antiviral therapy can be optimized by this concept; in addition we report treatment outcome of the first 40 patients who finished antiviral therapy and a 12-week follow-up period.

SETTING

PWID with chronic hepatitis C and borderline compliance receive interferon-free all-oral treatment of chronic hepatitis C together with Opioid Agonist Therapy under direct observation of a physician or nurse at the "Ambulatorium Suchthilfe Wien" – a low-threshold drug treatment facility in Vienna, Austria.

MATERIALS & METHODS

Assessment of fibrosis stage:
Prior to treatment fibrosis stage is classified according to the METAVIR scoring system (F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis and few septa; F3 = numerous septa without cirrhosis; F4 = cirrhosis) and assessed by transient elastography using the Fibroscan® 502 Touch device with the M-probe (Echosens, Paris, France). Cut-off values for liver stiffness (LS) were defined as 7.1 kPa for F ≥ 2, 9.5 kPa for F ≥ 3 and 12.5 kPa for F = 4. Only procedures with 10 successful measurements of liver stiffness with an interquartile range < 30% were considered reliable.

Antiviral treatment:
Two cohorts of patients are treated:
Cohort I: Treatment naïve, non-cirrhotic GT1 patients without coinfection with HIV or HBV are included into a non-interventional study (supported by Gilead Sciences) and treated with sofosbuvir/ledipasvir for eight weeks.
Cohort II: For all other patients the individual treatment regimen is selected according to genotype, fibrosis stage, pretreatment, HIV-status and current reimbursement policy of insurances.

So far 67 patients have started treatment of chronic hepatitis C (40 patients in cohort I and 27 patients in cohort II). The study population includes 52 males and 15 females, the mean age ± SD is 39.7 ± 9.2 years (range: 22 - 60), 52 patients are infected with genotype 1, 13 with genotype 3, one with genotype 2 and one with genotype 4. Four patients are coinfected with HIV. Compensated liver cirrhosis (F4) was diagnosed in 17 patients. Only three patients were pretreated with peginterferon plus ribavirin, all other patients were treatment-naïve.
The study was approved by the local Ethics Committee.

RESULTS

Adherence to therapy:
Adherence to therapy was excellent: Till now, only four out of 4.496 scheduled dates (0.09%), for ingestion of the antiviral therapy in combination with Opioid Agonist Therapy were missed by the 67 patients.

Virological outcome:
So far, 40 patients (25 from cohort I and 15 from cohort II) have finished treatment and a 12-week follow-up period. Baseline characteristics and treatment regimens of these patients are summarized in Table 1 (cohort I) and Table 2 (cohort II), respectively. Virological cure of hepatitis C virus infection, i.e. sustained virological response (SVR), could be documented in all 40 patients 12 weeks after end of therapy (SVR12 rate: 100.0%). No relapses were observed and no patient was lost to follow-up.
Additional 12 patients have finished treatment; PCR was negative in all of them at the end of therapy. Fifteen patients are still on treatment.

Serious adverse events:
No serious adverse events related to antiviral therapy were observed in any of the 67 patients.

Table 1: Baseline characteristics, treatment and clinical outcome in patients from cohort I

Patient number	Age (years)	Sex (m/f)	Geno-type	HIV Co-infection	Fibrosis stage	Treatment	Duration of therapy (weeks)	Outcome
1	46	m	1b	no	F0/F1	sofosbuvir/ledipasvir	8	SVR12
2	46	m	1b	no	F0/F1	sofosbuvir/ledipasvir	8	SVR12
3	43	m	1a	no	F3	sofosbuvir/ledipasvir	8	SVR12
4	39	m	1a	no	F2	sofosbuvir/ledipasvir	8	SVR12
5	44	m	1a	no	F2	sofosbuvir/ledipasvir	8	SVR12
6	34	f	1a	no	F0/F1	sofosbuvir/ledipasvir	8	SVR12
7	53	m	1a	no	F3	sofosbuvir/ledipasvir	8	SVR12
8	29	m	1a	no	F0/F1	sofosbuvir/ledipasvir	8	SVR12
9	36	m	1a	no	F2	sofosbuvir/ledipasvir	8	SVR12
10	30	m	1a	no	F0/F1	sofosbuvir/ledipasvir	8	SVR12
11	52	m	1a	no	F2	sofosbuvir/ledipasvir	8	SVR12
12	43	m	1a	no	F0/F1	sofosbuvir/ledipasvir	8	SVR12
13	25	m	1a	no	F0/F1	sofosbuvir/ledipasvir	8	SVR12
14	34	f	1a	no	F3	sofosbuvir/ledipasvir	8	SVR12
15	40	m	1a	no	F0/F1	sofosbuvir/ledipasvir	8	SVR12
16	34	f	1a	no	F2	sofosbuvir/ledipasvir	8	SVR12
17	31	f	1b	no	F0/F1	sofosbuvir/ledipasvir	8	SVR12
18	37	f	1a	no	F2	sofosbuvir/ledipasvir	8	SVR12
19	46	m	1b	no	F0/F1	sofosbuvir/ledipasvir	8	SVR12
20	25	f	1b	no	F2	sofosbuvir/ledipasvir	8	SVR12
21	47	m	1a	no	F3	sofosbuvir/ledipasvir	8	SVR12
22	36	m	1a	no	F2	sofosbuvir/ledipasvir	8	SVR12
23	28	m	1a	no	F0/F1	sofosbuvir/ledipasvir	8	SVR12
24	25	f	1a	no	F0/F1	sofosbuvir/ledipasvir	8	SVR12
25	36	f	1a	no	F0/F1	sofosbuvir/ledipasvir	8	SVR12

Table 2: Baseline characteristics, treatment and clinical outcome in patients from cohort II

Patient number	Age (years)	Sex (m/f)	Geno-type	HIV Co-infection	Fibrosis stage	Treatment	Duration of therapy (weeks)	Outcome
1	41	f	3	no	F4	sofosbuvir/daclatasvir	24	SVR12
2	46	m	3a	yes	F4	sofosbuvir/daclatasvir	24	SVR12
3	37	m	3a	no	F4	sofosbuvir/daclatasvir	24	SVR12
4	48	m	1b	yes	F3	sofosbuvir/ledipasvir	12	SVR12
5	32	m	1a	no	F4	sofosbuvir/ledipasvir	12	SVR12
6	31	m	1a	yes	F4	sofosbuvir/ledipasvir	12	SVR12
7	40	m	3a	no	F3	sofosbuvir/daclatasvir	12	SVR12
8	30	m	4	no	F2	paritaprevir/ombitasvir plus ribavirin	12	SVR12
9	45	m	1a	no	F4	sofosbuvir/ledipasvir	12	SVR12
10	55	m	3	no	F4	sofosbuvir/daclatasvir	24	SVR12
11	39	m	1a	no	F4	sofosbuvir/ledipasvir	12	SVR12
12	27	m	3a	yes	F2	sofosbuvir/ledipasvir plus ribavirin	12	SVR12
13	28	m	3a	no	F4	sofosbuvir/daclatasvir	24	SVR12
14	58	m	1a	no	F4	sofosbuvir/ledipasvir	12	SVR12
15	37	m	3a	no	F2	sofosbuvir/ledipasvir plus ribavirin	12	SVR12

DISCUSSION

Persons receiving Opioid Agonist Therapy represent a very heterogeneous group of patients: Patients with good compliance can be referred to and treated at hepatologic centers. A second group, however, is characterized by a borderline compliance and a high prevalence of psychiatric comorbidity. In the past chronic hepatitis C in this subgroup of patients could not be treated because of two reasons: First, interferon-based treatment regimens were contraindicated because of concomitant psychiatric disorders. Second, these patients are reluctant to go to specialized hepatologic centers and hence cannot be treated there. The concept presented in this paper overcomes these two problems: With modern direct acting antivirals chronic hepatitis C can be cured without relevant side effects in nearly 100% of patients and concomitant psychiatric disorders are no limitation for therapy anymore. As compliance of these patients is excellent with respect to their daily visits at a low-threshold facility or pharmacy, chronic hepatitis C can be treated by applying interferon-free all-oral regimens together with Opioid Agonist Therapy under direct observation of a physician or nurse at a low-threshold drug treatment facility.
It should be stressed that successful treatment of chronic hepatitis C in PWID is not only beneficial for themselves but also for the general population because transmission of the virus is prevented. An approach similar to the concept presented in this paper has shown to be effective in treatment of HIV in PWID.

CONCLUSION

We conclude that directly observed therapy of chronic hepatitis C with interferon-free regimens at a low-threshold drug treatment facility is a promising new concept for treatment of patients with borderline compliance receiving Opioid Agonist Therapy.

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