Reaching the Unreachable: Strategies for HCV Eradication in Patients With Refractory Opioid Addiction—A Real-world Experience

Lisa Sandmann,1,10 Julian Deppe,1,23 Christoph Beier,1 Valerie Ohlendorf,1 Julia Schneider,1 Heiner Wedemeyer,14 Felix Wedegärtner,1 Markus Cornberg,1,15 and Benjamin Maasoumy1,15

1Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany, 2Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany, 3Patricia Medizinisches Versorgungszentrum, Hannover, Germany, 4German Center for Infection Research (DZIF), Partner Site Hannover-Braunschweig, Hannover, Germany, and 5Centre for Individualised Infection Medicine (CiiM), Helmholtz Centre for Infection Research, Hannover, Germany

To achieve global hepatitis C virus (HCV) eradication, barriers prohibiting access need to be overcome. We established a strategy to initiate antiviral therapy in patients with severe, refractory heroin addiction. All patients achieved sustained virological response. Outreach programs of hepatologists might be a reasonable way to overcome barriers to HCV treatment.

Keywords. active drug use; DAA; diamorphine; HCV; heroin.

Since the introduction of direct-acting antivirals (DAAs), treatment of chronic hepatitis C virus (HCV) infection has been well tolerated and highly effective. Therefore, the World Health Organization (WHO) has set the goal of eradicating HCV infection by 2030 [1]. To achieve this aim, treating chronic HCV infection in populations with a high prevalence of HCV is essential. People who inject drugs (PWID) are highly affected by chronic HCV infection. In this population, anti-HCV prevalence is estimated to be 52.3% globally [2]. In Germany, anti-HCV prevalence in the PWID population ranges from 63% to 68% [3]. It has been shown that antiviral treatment is safe and effective for PWID with moderate addiction disorder who can be managed with opioid agonist maintenance therapy (OAT) [4–6]. However, patients with documented active drug use have rarely been included in such trials [5, 7, 8]. Moreover, data on those with severe, refractory addiction are scarce. People with ongoing intravenous drug use suffer from multiple comorbidities and difficulties with regard to integration into the regular health care system. At the same time, rates of chronic HCV infection are high and antiviral treatment is urgently needed, for both individual [9] and public health benefit [10]. However, initiation of antiviral treatment has been shown to be hindered at multiple levels. Implementation of HCV testing, linkage to hepatologist care, lack of on-site delivery of HCV treatment, and completion of therapy are examples of gaps that have been identified by several studies [11, 12]. To overcome these barriers, novel treatment approaches are needed. Therefore, we developed a local treatment strategy in cooperation with the outpatient clinic for heroin-assisted treatment (HAT) to deliver HCV treatment to patients with severe opioid dependency.

METHODS

The outpatient clinic for HAT in Hannover offers treatment with intravenous diamorphine for patients with severe, refractory heroin addiction who have previously failed conventional substitution treatment. Patients visit the outpatient clinic on a daily basis to receive diamorphine treatment managed by psychiatrists who specialize in addiction medicine. In cooperation with the psychiatrists, we established a strategy to initiate antiviral therapy in these patients: Anti-HCV and HCV-RNA-positive patients were identified by the psychiatrists during routine assessment. The hepatologist team visited the outpatient clinic for baseline visit. Decompensated liver cirrhosis was excluded based on clinical and basic laboratory values. Due to the use of pangenotypic DAA treatment with sofosbuvir/velpatasvir, HCV genotyping was abdicable. Laboratory tests were reduced to a minimum to minimize blood withdrawal procedures and were only performed before baseline to verify ongoing viral infection and 12 and 96 weeks after the end of treatment to assess SVR and re-infection (all on-site). Antiviral treatment was carried out on-site by the psychiatrists, and the hepatologist team provided consultation if needed. No additional medical appointments were necessary for the patients. It was the patient’s choice whether to manage their DAA treatment independently or with the support of the HAT team. Health-related quality of life (HRQOL) was assessed by the SF-36 questionnaire before and after the end of DAA treatment (Figure 1A).

Statistical analyses were performed using Excel (version 16.37 for Windows, Microsoft, Redmond, WA, USA), GraphPad Prism (version 7.05 for Windows, GraphPad Software, La Jolla, CA, USA), and SPSS (version 26, SPSS Inc, Chicago, IL, USA).
Forty-five patients with refractory heroin addiction were treated in the HAT clinic. Anti-HCV antibody was detected in more than one-third of the patients (n = 17/45), and the vast majority had chronic HCV infection (82%, 14/17). Antiviral treatment was offered to all viremic patients. However, 5 patients did not start DAA therapy for various nonhepatic reasons: 2 experienced imprisonment, 2 discontinued HAT, and 1 decided against DAA treatment (Figure 1B). Patients were predominantly male (89%). Six patients (70%) were anti-HBc positive, but HBsAg was negative in all patients. Four patients (44%) were at risk of liver cirrhosis based on aspartate transaminase to platelet ratio index (APRI) score, but liver disease was compensated in all patients (Table 1).

In patients starting antiviral treatment, infection had been known for a median of 11 years (min 4, max 30). All patients were aware of their infection, but only 1 patient had previously been treated with an interferon-based regimen. "Fear of interferon side effects" was the most prevalent reason for not commencing antiviral treatment before (n = 5/9, 56%). The availability of DAA therapy was already known by 78% (n = 7/9) of the patients. All patients reported parallel consumption of additional drugs including alcohol (44% with harmful use), and all but 2 patients named the HAT outpatient clinic as their primary medical contact (no additional primary care physician). The rate of psychiatric comorbidities was 100% (n = 9/9).

All but 1 patient decided to take the daily DAA dose during their visit to the outpatient clinic. During DAA therapy, no side effects were reported. All patients who started treatment

Table 1. Baseline Characteristics

| Total (n = 9) |  |
|---|---|
| Gender, male | 8/9 (89) |
| Age, y | 47 ± 8.6 |
| HCV RNA, log IU/mL | 6.16 ± 0.9 |
| Anti-HBc pos. | 6/9 (66.7) |
| HBsAg pos. | 0/9 (0) |
| Anti-HBs pos. | 5/9 (55.6)* |
| ALT U/L | 60.4 ± 25.3 |
| Bilirubin, µmol/L | 10.8 ± 6.1 |
| Creatinine, µmol/L | 75 ± 20.5 |
| Thrombocytes, tsd/µL | 183 ± 95.6 |
| INR | 0.94 ± 0.08 |
| APRI score | 0.95 ± 0.47 |
| APRI >1 | 4/9 (44.4) |

Categorical data are expressed as No. (%). Continuous data are expressed as mean ± SD. Abbreviations: ALT, alanine transaminase; APRI, AST to platelet ratio index; AST, aspartate transaminase; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio.

*HBV reactivation for the 2 anti-HBc-positive, anti-HBs-negative patients was excluded by normal ALT levels and negative HBV DNA at the end of treatment.
completed therapy and achieved SVR (mITT: 9/9, 100%; ITT: 9/14, 64%) (Figure 1B). No re-infection occurred during 96 weeks of follow-up.

HRQOL was assessed by the SF-36 questionnaire. Patients' scores on the physical and mental subscales were overall lower compared with the population norm irrespective of treatment status. When compared with the German norm population with addiction disorder, scores in all subscales except “Bodily Pain” were lower in our cohort before antiviral treatment. However, 24 weeks after the end of treatment, all subscale scores except for “Role Emotional” were higher than or similar to this norm population. Overall, subscales measuring physical and mental characteristics improved 24 weeks after the end of treatment (Figure 1C). The increases exceeded 5% (which is considered to be a meaningful clinical change) [13] in 7 of the 8 domains and included a 33% improvement on the Vitality scale, which has been identified as the HRQOL domain of the SF-36 that is most relevant to chronic HCV infection [14].

**DISCUSSION**

In our study, we established a real-life treatment concept to deliver antiviral treatment of chronic HCV infection to patients with severe, refractory opioid dependency. We showed that antiviral treatment is feasible, well tolerated, and successful in patients on HAT. This is in line with findings from the interferon era that showed comparable viral response rates between severely opioid-dependent patients on HAT and non-drug users [15]. Moreover, the efficacy of DAA in PWID with less severe addiction disorder, that is those stable on OAT, has been demonstrated by multiple studies [5, 16, 17]. Viral eradication causes several positive effects: First, the risk of hepatic deterioration due to HCV infection is removed [9]. Second, patients experience improvement in HRQOL [18, 19]. Furthermore, individual viral eradication leads to a reduction of the general burden of HCV infection and reduces further viral spreading [20, 21]. Despite its positive effects, implementation of antiviral treatment in the PWID population remains insufficient. The reasons for this are multilayered and include system-, provider-, and patient-related factors. In our cohort, patients reported fear of treatment-related side effects and lack of motivation as the main reasons for not having started treatment before. Additionally, perceived lack of capability to initiate treatment autonomously, the burden of addiction disorder itself, and stigmatization were named as general reasons for not starting treatment. Similar aspects emerged in the study by Skeer et al., who additionally identified “perceived lack of referral to treatment”, “lack of care continuity”, and the perceived need for treatment including “lack of deservingness of treatment” as barriers to care [22]. Despite being aware of their infection, most patients do not perceive liver disease as the medical problem most urgently in need of addressing [22]. This is mainly due to their immense psychiatric comorbidity and concomitant social difficulties, which more directly affect the patients’ everyday life. Due to the compounding mental symptom load in patients with severe addiction disorder, a multidisciplinary treatment approach is needed to successfully offer antiviral treatment. The setting of HAT and OAT allows contact with this difficult-to-reach population on a regular basis. Still, physicians involved in addiction units are not usually trained in HCV care, and successful referral to specialized outpatient clinics is not feasible in most cases. Therefore, on-site antiviral treatment emerges as the best option for these patients. In our cohort, the HAT outpatient clinic served as the main medical contact for the patients, and on-site treatment was facilitated in several ways. Appointments were flexible, and patients benefited from familiar clinical staff. Antiviral treatment was explained and initiated by the hepatologist team but conducted by the on-site psychiatric team. No additional appointments were necessary for the patients. This multidisciplinary treatment approach and the continuity of care are important factors facilitating antiviral treatment in this population [7]. For our real-world study, it can be assumed that without the on-site treatment approach, patients would probably not have started antiviral treatment in the medium term.

Despite the single-center experience and the overall low number of treated patients, our study offers several insights: It shows that by establishing a multiprofessional on-site treatment approach, comparably high rates of treatment uptake and viral clearance are achieved. Importantly, patients at high risk of further delaying or never starting antiviral treatment were linked to care. The study might serve as an example not only to motivate other patients to start antiviral therapy but also to encourage medical professionals to develop multidisciplinary strategies to overcome treatment barriers.

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**Patient consent.** All patients agreed to the usage of their data after anonymization. Data analysis of HCV treatment has been approved by the ethics committee of Hannover Medical School (No. 9227).

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