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BRIEF REPORT

Concomitant Treatment of Chronic Hepatitis C With Direct-Acting Antivirals and Multidrug-Resistant Tuberculosis Is Effective and Safe

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We assessed effectiveness and safety of concomitant chronic hepatitis C virus (HCV) treatment with direct-acting antivirals (DAAs) and multidrug-resistant tuberculosis (MDR-TB). Of 322 MDR-TB patients (19.4% HCV), 30 were treated concomitantly (23.3% human immunodeficiency virus-positive). Overall, 76.7% achieved HCV treatment success (95.8% among tested). One patient (3.3%) experienced a serious adverse event.

Keywords. chronic hepatitis C virus; direct-acting antiviral drugs; multidrug-resistant tuberculosis; sofosbuvir.

Multidrug-resistant tuberculosis (MDR-TB) and hepatitis C virus (HCV) infection are 2 alarming public health threats [1, 2]. Multidrug-resistant tuberculosis patients coinfected with HCV are more likely to develop drug-induced liver injury [3], one of the most common adverse events (AEs) during MDR-TB treatment with reported rates at 9.7%–22.3% [3–5]. Hence, the treatment of HCV coinfection patients with MDR-TB might be beneficial. The safety and effectiveness of direct-acting antivirals (DAAs) for the treatment of HCV infection have been evaluated in clinical trials and real-life settings [6–11]. However, to our knowledge, there are no studies assessing the safety and effectiveness of providing DAA treatment to patients also being treated for MDR-TB. The only evidence available is 2 case reports from Italy [12].

In Armenia, the seroprevalence of HCV is estimated at 4% in the general population [13]. In 2016, Médecins Sans Frontières (MSF) facilitated the use of DAAs to treat MDR-TB patients with chronic HCV infection in the country. The objective of this study was to assess the prevalence of chronic HCV infection among MDR-TB patients in Armenia and the safety and effectiveness of the concomitant treatment of chronic HCV infection with DAAs and MDR-TB disease.

MATERIALS AND METHODS

Study Design and Population

This observational study included consecutive MDR-TB patients over 18 years diagnosed with chronic HCV infection from January 2016 until December 2018 in Armenia. Patients were observed until June 2019. Data on effectiveness and safety are reported from patients who received concomitant DAAs and MDR-TB treatment only.

Study Procedures

From January 2016, HCV diagnosis with HCV antibody test (enzyme-linked immunosorbent assay or rapid test) followed by HCV polymerase chain reaction (PCR) test was offered to all patients on or starting MDR-TB treatment in Armenia. From December 2016, treatment with DAAs including 12 weeks of daclatasvir 60 mg/sofosbuvir 400 mg (DCV/SOF) or ledipasvir 90 mg/sofosbuvir 400 mg (LDV/SOF) was offered to patients with chronic HCV infection. The dose of DCV was increased to 90 mg when coadministered with efavirenz or nevirapine. The duration of treatment was extended to 24 weeks, and ribavirin (RBV) was added to the regimen in patients with genotype 3a and advanced fibrosis on FibroScan (>14.5 kPa). Exclusion criteria to start DAA included the following: end stage liver disease, evidence of hepatocellular carcinoma, presence of terminal disease, human immunodeficiency virus (HIV) viral load above 1000 copies/mL, severe, uncontrolled psychiatric disease and baseline hemoglobin below 9 g/dL for regimens containing RBV.

Before DAA start, all patients underwent initial assessment including the following: medical history, clinical evaluation, grading of fibrosis, testing for HCV genotype, HBsAg and anti-HBc antibodies, HIV, CD4 count, HIV viral load, pregnancy, complete blood count, liver enzymes, bilirubin, creatinine, glucose, and ultrasound. Endoscopy was indicated if FibroScan >20 kPa and platelets <150 000 cells/μL (none of the patients met these criteria). Monthly follow-up was performed throughout the HCV treatment and at 12 weeks after treatment completion and included clinical evaluation, complete blood

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count, liver enzymes, bilirubin, and creatinine. Hepatitis C virus PCR was performed at the end of DAA treatment and 12 weeks posttreatment. Adverse events deemed to be of clinical significance were identified and reported by treating doctors based on clinical assessment and laboratory results. Patients who started DAA treatment after May 2018 were followed prospectively, and patient files of those who started DAAs before this date were reviewed retrospectively.

Definitions

Chronic HCV infection is defined as positive HCV antibody and positive HCV PCR. Sustained virological response 12 weeks after treatment completion (SVR12) is defined as follows: at least 1 HCV ribonucleic acid result undetectable or viral load concentration below 12I U/mL 12 weeks after the end of treatment. This was the measure of HCV treatment success. Treatment failure was defined as detectable viral load at 12 weeks posttreatment.

Adverse events deemed to be of clinical significance were as follows: creatinine clearance <50 mL/mm, alanine aminotransferase and/or aspartate aminotransferase levels >5 times of upper limit of normal, any AE that resulted in a temporary interruption, permanent discontinuation, or change in the dose of 1 or more DAA or MDR-TB drug as decided by the doctor. Serious AEs (SAEs) were defined as events that resulted in death or significant disability, were life-threatening, or required hospitalization.

Data Analysis

We perform descriptive analyses to characterize the population and determine proportions of patients that achieved SVR12 or had an AE. The effectiveness endpoint was the proportion of participants with SVR12 among patients who started DAAs and among those tested with HCV PCR. The safety endpoint was the frequency of AEs of clinical significance and SAEs that occurred during DAA treatment and 12 weeks posttreatment. Analyses were done using Stata 13 (StataCorp College Station, TX).

Ethics

The study protocol was approved by the MSF Ethics Review Board (ERB) and the Yerevan State Medical University Ethics Committee in Armenia. Written informed consent was obtained from patients enrolled prospectively and from patients under care enrolled retrospectively. The ERBs waived consent provision from patients enrolled retrospectively who were no longer under follow-up for MDR-TB.

RESULTS

Patients' Flow and prevalence of HCV infection

From January 2016 to December 2018, 322 adult patients started MDR-TB treatment in Armenia. Hepatitis C virus antibody test was positive in 29.3% (78 of 266) and HCV PCR was positive in 71.4% (50 of 70) of them. Overall, among the MDR-TB patients tested, 19.4% (50 of 258; 95% confidence interval, 14.7–24.7) had chronic HCV infection. An additional 20 patients were diagnosed with chronic HCV infection during the study period among patients who had started MDR-TB treatment before 2016 (Figure 1). In total, 40 of 70 (60.6%) started DAA treatment during the study period (Figure 1). Of the 40 patients treated, 30 received concomitant DAA and MDR-TB treatment, whereas 10 had already completed MDR-TB treatment when DAA treatment was initiated.

Patient Characteristics

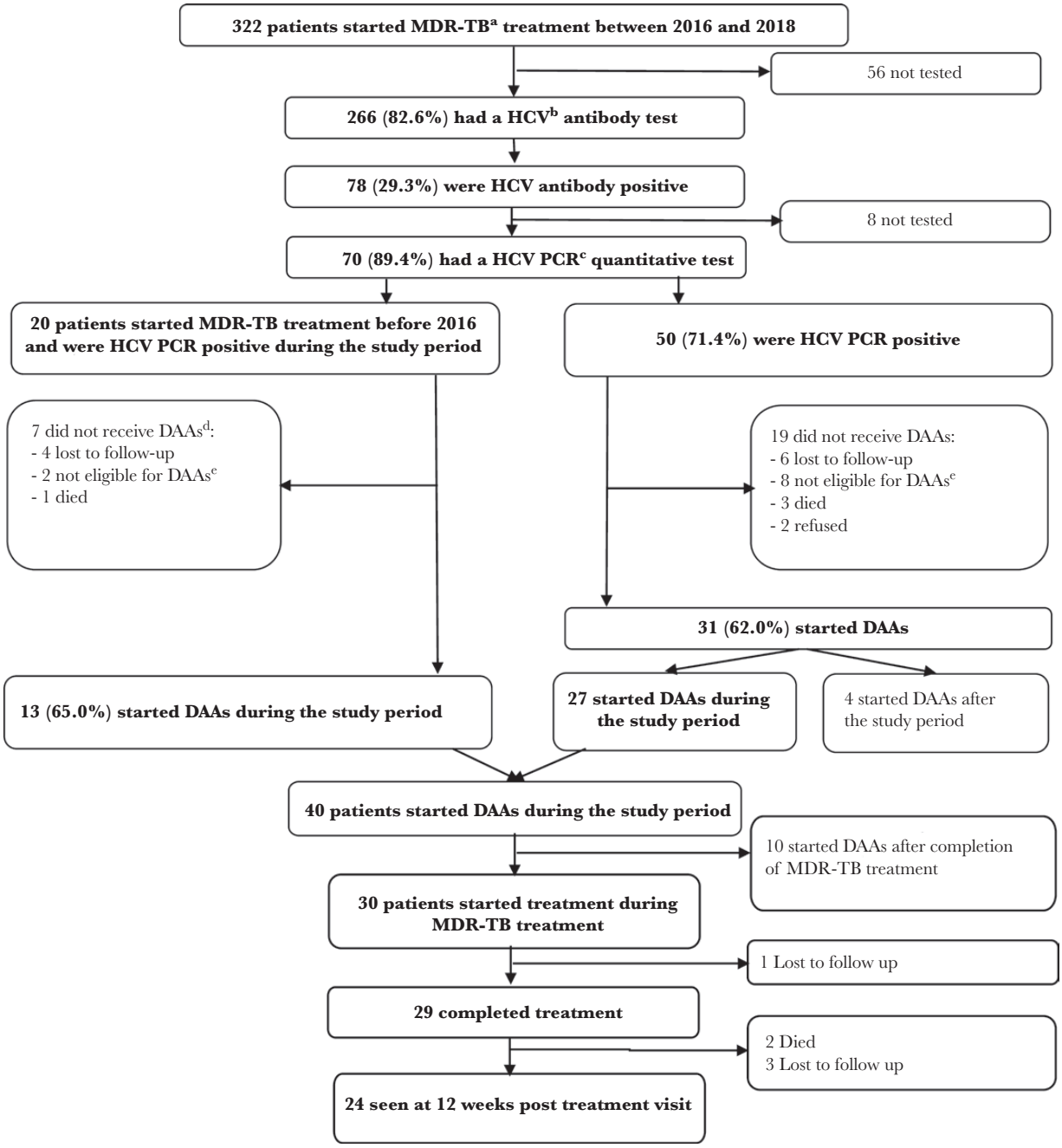
Table 1 shows the characteristics of the 30 patients who received concomitant DAAs and MDR-TB drugs. Median age was 51.5 years, 96.7% were men, and 23.3% HIV positive. All patients were DAA treatment naive. The median time from MDR-TB treatment initiation to the start of DAAs was 5.4 (interquartile range, 2.1–12.1) months. At DAA treatment start, all HIV-positive patients were receiving antiretroviral therapy and were virally suppressed. The majority of the patients (26 of 30, 86.7%) were treated with 12 weeks of DCV/SOF irrespective of the genotype. Two (6.7%) patients with genotype 3a and advanced fibrosis received 24 weeks of DCV/SOF/RBV. Two patients (6.7%) with genotype 1b received 12 weeks of LDV/SOF. No patients had liver lesions attributable to TB.

Effectiveness

SVR12 was achieved in 76.7% (23 of 30) of the patients who initiated DAAs. Among patients who were tested at 12 weeks posttreatment, 95.8% (23 of 24) achieved SVR12. One (4.2%) patient experienced DAA treatment failure. This patient was HIV positive, had genotype 3a HCV infection, stage F0-F1 hepatic fibrosis, and was prescribed 12 weeks of DCV/SOF. Hepatitis C virus PCR was not done at 12 weeks for 6 patients, 4 of whom had a HCV PCR test done at the end of treatment, all with negative results.

Safety

During concomitant treatment with DAA and MDR-TB drugs, 1 patient (3.3%) experienced a SAE and 4 (13.3%) experienced AEs of clinical significance. The SAE was reported by the treating doctor as possibly related to DAAs. This patient experienced a severe allergic reaction 16 days after initiation of DAA treatment with DCV/SOF, which led to temporary interruption of the DAAs and MDR-TB drugs and resolved after treatment with antihistamine drugs. Both HCV infection and MDR-TB treatments were completed successfully. The 4 AEs of clinical significance were reported as related to the TB drugs. From DAA treatment completion until 12 weeks posttreatment, no AEs related to the DAA treatment were reported.



[a]MDR-TB, multidrug-resistant tuberculosis; [b]HCV, hepatitis C virus; [c]PCR, polymerase chain reaction; [d]DAAs, direct-acting antivirals.
[e]Patients not eligible (or not prioritized at the beginning of the program due limited supply of DAAs): 4 with detectable HIV viral load, 1 end stage liver disease, 3 MDR-TB treatment already completed, 1 severe condition, 1 unknown reason. Outcomes of the patients not eligible: 4 died, 6 lost to follow-up.

Figure 1. Study patient flow.

DISCUSSION

In a context of high prevalence of chronic HCV infection among MDR-TB patients, HCV treatment success was achieved in a high proportion of patients treated concomitantly with DAAs and MDR-TB drugs with no major safety problems. To our knowledge this is the first study reporting concomitant use of DAAs and MDR-TB drugs. The effectiveness results found are consistent with treatment success rates reported in clinical and observational studies of LDV/SOF and DCV/SOF±RBV use among non-TB patients [6–11, 14].

In our study, the patient who experienced DAA treatment failure was HIV positive, had HCV genotype 3a infection,

Table 1. Sociodemographic and Clinical Characteristics and Adverse Events in Patients With Chronic Hepatitis C Who Received DAAs With MDR-TB Drugs Concomitantly (N = 30)

Characteristics	Patients Started DAA[a], n (%)
Age (median in years, IQR)	52 (41–56)
Body mass index <18.5 kg/m^2	6 (20.0)
Men	29 (96.7)
Incarceration (former or current)	16 (53.3)
Alcohol consumption (current)	15 (50.0)
Intravenous drug user (former or current)	11 (36.7)
Comorbidities	
- HIV positive	7 (23.3)
- Anti-HBc-total positive (N = 28)	9 (32.1)
HCV Genotype	
- 1b	9 (30.0)
- 2	4 (13.3)
- 3a	15 (50.0)
- 4	1 (3.3)
- Indeterminate	1 (3.3)
FibroScan	
- F0-F1 (2.5–7.0 kPa)	22 (73.3)
- F2 (7.1–9.4 kPa)	3 (10.0)
- F3 (9.514.5 kPa)	2 (6.7)
- F4 (>14.5 kPa)	3 (10.0)
Antiretroviral Therapy	
Tenofovir	5 (16.7)
- Efavirenz, nevirapine	6 (20.0)
- Emtricitabine, abacavir, lamivudine	9 (30%)
- Lopinavir/ritonavir	2 (6.7)
MDR-TB Drugs	
Group A	
- Levofloxacin	18 (60.0)
- Linezolid	16 (53.3)
- Bedaquiline	6 (20.0)
- Moxifloxacin	5 (16.7)
Group B	
- Cycloserine	26 (86.7)
- Clofazimine	19 (63.3)
Group C	
- Delamanid	13 (43.4)
- *p*-aminosalicylic acid	13 (43.3)
- Prothionamide	12 (40.0)
- Pyrazinamide	8 (26.7)
- Imipenem/cilastatin	6 (20.0)
- Kanamycin	4 (13.3)
- Capreomycin	4 (13.3)
Adverse Event[a]	
Serious adverse events (SAE)	1 (3.3)
Adverse events of clinical significance (not SAE)	4 (13.3)
Adverse events possibly related to DAA	1 (3.3)
Adverse events leading to temporary DAA discontinuation	1 (3.3)

Abbreviations: DAAs, direct-acting antivirals; HB, hepatitis B; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; MDR-TB, multidrug-resistant tuberculosis.

[a]Adverse events: 1 allergic reaction (severity grade 3, SAE), 1 anemia (severity grade 2), 1 dizziness (severity grade 1), 1 peripheral neuropathy (severity grade 1), 1 platelet decrease (severity grade 1).

without advanced liver damage (stage F0-F1), and was prescribed 12 weeks of DCV/SOF. A possible contributing factor to DAA treatment failure could be poor adherence because the patient interrupted MDR-TB treatment for 3 weeks while on DAAs and possibly could have also interrupted DAAs. The genotype 3a is a subtype of HCV infection with lower response rates [10] when accompanied with cirrhosis [11], although this was not the case for this patient.

The concomitant use of DAA with second-line antituberculosis drugs was well tolerated. Data on interactions between DCV, LDV, and SOF and second-line antituberculosis drugs are very limited. Theoretically, ethionamide/prothionamide and clofazimine can interact with DCV because both are CYP3A4 inhibitors in vitro. However, the clinical relevance is unknown. Concomitant use of the first-line antituberculosis drug rifampicin and DAAs is not recommended [15]. Overall, the rate of untoward medical occurrences in this cohort of patients (2.6%) was not higher than described in experimental and nonexperimental settings [6, 9–11].

The study has some limitations. It was not possible to evaluate whether HCV treatment could reduce hepatotoxicity during MDR-TB treatment in coinfected patients due to the limited number of participants. In addition, some patients did not have a viral load measurement 12 weeks posttreatment. However, almost all of them had a measurement at the end of the DAA treatment.

CONCLUSIONS

This novel study shows that DAAs can be successfully used to treat chronic HCV infection in MDR-TB patients without major safety concerns. Further research with more participants is needed to generate additional evidence on the safety and effectiveness of the concomitant use of DAAs with second-line antituberculosis drugs. The colocation of the HCV/MDR-TB care is an important step towards patient-centered care and the achievement of the HCV elimination goal.

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