

ORIGINAL ARTICLE

Directly observed therapy for chronic hepatitis C: A randomized clinical trial in the prison setting



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Abstract

Background: The diagnosis and treatment of chronic hepatitis C are major concerns in prisons. **Objectives:** The aim of this randomized clinical trial was to determine the extent to which directly observed therapy (DOT) improved the efficacy of the standard treatment for chronic hepatitis C in the prison setting.

Patients and methods: A randomized clinical trial was carried out to evaluate the efficacy of a DOT compared with a self-administered therapy in prison inmates who underwent standard treatment for chronic hepatitis C (based on pegylated interferon alpha-2a and ribavirin).

Results: A total of 252 inmates were randomized, of which 244 were analyzed: 109 in the DOT group and 135 in the non-DOT group. The mean age was 35.88 years (SD 6.54), 94.3% were men, 72.1% reported intravenous drug use, 21.3% were HIV co-infected, and 55.3% had genotype 1 or 4. The patients received the study treatment for a median time of 33.9 weeks in the overall sample. Sustained virological response was achieved in 60.6% (95% CI, 51.17–69.22) of the DOT group and in 65.9% (95% CI, 57.59–73.38) of the standard therapy group (risk ratio = 0.92; 95% CI, 0.76–1.12). The mean proportion of patients continuing the treatment was 83% (SD = 31). Adverse events were reported in 93.4% of the patients, and serious adverse events were reported in 8.2%, with no significant differences between groups.

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PALABRAS CLAVE

Hepatitis C crónica;
Tratamiento
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Ribavirina

Conclusions: Sustained virological response was remarkably high, although there were no differences between groups, probably due to high treatment adherence.

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Tratamiento directamente observado de la hepatitis C crónica: un ensayo clínico aleatorizado en el ámbito penitenciario

Resumen

Antecedentes: El diagnóstico y tratamiento de la hepatitis C crónica son una preocupación importante en los centros penitenciarios.

Objetivos: El propósito de este ensayo clínico aleatorizado fue determinar hasta qué punto el tratamiento directamente observado (TDO) mejoraba la eficacia del tratamiento estándar para la hepatitis C crónica en el ámbito penitenciario.

Pacientes y métodos: Ensayo clínico aleatorizado para evaluar la eficacia del TDO comparado con el tratamiento auto-administrado en internos que reciben régimen estándar para la hepatitis C crónica (interferón pegilado alfa-2a y ribavirina).

Resultados: Se aleatorizaron un total de 252 sujetos, de los cuales se analizaron 244: 109 el grupo TDO y 135 en el grupo no-TDO. La media de edad fue 35,88 (DE 6,54), 94,3% eran hombres, 72,1% eran usuarios de drogas intravenosas, 21,3% co-infectados con HIV y 55,3% tenían genotipo 1 o 4. En la muestra global, los pacientes recibieron el tratamiento del estudio durante una mediana de tiempo de 33,9 semanas. La respuesta virológica sostenida se alcanzó en un 60,6% (IC 95%, 51,17 a 69,22) de los pacientes del grupo TDO y 65,9% (IC 95%, 57,59 a 73,38) en el grupo no-TDO (Riesgo Relativo = 0,92; IC 95%, 0,76 a 1,12). La proporción media de continuidad del tratamiento fue 83% (DE = 31). Se comunicaron eventos adversos en un 93,4% de los pacientes, y en un 8,2% de los pacientes se notificaron eventos adversos graves, sin diferencias significativas entre ambos grupos.

Conclusiones: La respuesta virológica sostenida fue llamativamente elevada, aunque no hubo diferencias entre grupos, probablemente debido a la elevada adherencia al tratamiento en las dos ramas.

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Introduction

The prevalence of hepatitis C virus (HCV) infection in incarcerated population is 10–20 times higher than in the general population and ranges between 30% and 40%.^{1,2} The high-risk behavioral patterns of the prison inmates, especially intravenous drug use (IDU), account for a substantial proportion of the high HCV prevalence observed within this setting.² In Spain, though the HCV prevalence among prison inmates has declined during recent years,^{3,4} it remains markedly higher than in the general population [23–34%].^{4,5}

Whether the HCV is eradicated spontaneously or persists is determined, among other factors, by the immune response of the host.⁶ However, chronic hepatitis develops in 75%–85% of the people infected with HCV, of whom 60%–70% develop active liver disease.⁷ Risk factors that accelerate the complications of chronically infected subjects, such as injected drug use, co-infections and alcohol use, are common among prison inmates. This risk profile explains the high HCV-related mortality reported in correctional facilities.⁸ Therefore, diagnosis and treatment of chronic hepatitis C are major concerns in prisons which led to the elaboration

of a consensus document to help healthcare professionals deal with HCV infection in prisons.⁹

Therapy adherence improves the treatment efficacy of chronic hepatitis C.¹⁰ Therefore, interventions, such as the directly observed therapy (DOT), which can be easily implemented in the prison setting, may increase the sustained virological response (SVR). To the best of our knowledge, the benefit that this intervention may provide in the prison setting has only been studied in a retrospective and non-comparative study.¹¹ Therefore, we performed a randomized clinical trial to determine to what extent DOT could improve the efficacy of the standard treatment for chronic hepatitis C in the prison setting.

Patients and methods

This was a multicenter, randomized, open clinical trial to evaluate the efficacy of a DOT compared with a self-administered therapy in prison inmates who underwent standard treatment for chronic hepatitis C (based on pegylated interferon alpha-2a and ribavirin).

Patients and setting

The study took place in the healthcare centers of 25 prisons in Spain, from July 2006 to September 2008. Eligible participants were prison inmates, men or women, aged over 18 years with chronic hepatitis C that were not previously treated. Prior to inclusion in the study, infection with HCV was confirmed by the presence of a positive antibody to HCV and a positive HCV RNA polymerase chain reaction result (HCV RNA >600 UI/mL). Liver biopsy was not mandatory and was only performed if performed routinely at the centers. To be eligible, a Child–Pugh score of 5 was required.^{12,13} In addition, within the 2 months before randomization, cirrhotic patients had an abdominal ultrasound, CT scan or MRI without evidence of hepatocellular carcinoma as well as a serologic test that showed alpha-fetoprotein (PFA) <100 ng/mL. Patients were ineligible if they had undergone any systemic antiviral, antineoplastic or immunomodulator therapy in the 6 months prior to the first dose of the study treatment or any investigational therapy in the 6 weeks prior to the first dose of the study treatment. Patients with the following comorbidities were also excluded: hepatic disease of an etiology other than HCV; positive IgM anti-HAV test; decompensated hepatic disease (Child–Pugh >6); prior transplantation with a current functional graft; high risk of anemia, coronary disease or cerebrovascular disease that, according to investigator criteria, were unlikely to tolerate an acute hemoglobin reduction (down to 4 g/dL); history of severe cardiac disease, thyroid disorder or abnormalities in thyroid function tests, unless they could be controlled with conventional treatment; and other severe comorbid conditions, such as chronic respiratory disease, immunological disease, severe retinopathy, severe psychiatric disorders or convulsive disorder. Women were also excluded if they were pregnant or lactating, as was each man whose partner was pregnant. Patients were excluded in case of neutropenia (neutrophil count <1500 cells/mm³), thrombocytopenia (platelet count <90,000 cells/mm³), anemia (hemoglobin concentration <12 g/dL) or serum creatinine level over 1.5 times the upper limit of normal. Finally, those patients with a history of drug use (including alcohol) in the previous year were excluded, except those who were already on methadone maintenance programs.

All patients provided written informed consent prior to entering the study. In accordance with local regulations, the study was approved by the ethics committee of the General University Hospital of Alicante (Spain) and the correctional competent authorities. The study was carried out according to the international ethical recommendations of the Declaration of Helsinki and Oviedo Convention, and according to the Guidelines of Good Clinical Practice and current Spanish legislation for clinical trials (Royal Decree 223/2004). Handling, communication and disposal of personal data for all participating individuals were performed according to Organic Law 15/1999, 13 of December, regarding the protection of personal data.

A random allocation sequence was generated centrally by the sponsor, using a prefixed randomization list, and communicated to the investigator each time a new patient was enrolled. Randomization was stratified based on the following variables: HCV genotype (1–4/2–3), viral load (high/low), ALT level (normal/abnormally high) and HIV

co-infection (yes/no). The investigator was responsible for assigning each patient to the randomly allocated intervention.

Intervention

All patients received standard treatment for hepatitis C based on pegylated interferon alpha-2a and ribavirin and were randomly assigned in a 1:1 ratio to either direct observed therapy (DOT group) or self-administered therapy (non-DOT group). In the DOT group, ribavirin was given by the study nurse, whereas in the non-DOT group, the ribavirin was self-administered. In both groups the subcutaneous injections of pegylated interferon alpha-2a were administered by the study nurse.

All patients received subcutaneous, once-weekly injections of 180 µg of pegylated interferon alpha-2a for either 48 weeks or 24 weeks. Patients were given oral ribavirin at a dose of 1000 mg/day (patients weighing 75 kg or less) or 1.200 mg/day (those weighing more than 75 kg) for 24 weeks (patients with genotype 2 or 3) or 48 weeks (patients with genotype 1 or 4). Patients without HIV co-infection and with genotype 2 or 3 received a fixed dose of ribavirin (800 mg/day) for 24 weeks. The participants were followed for 24 additional weeks after treatment cessation. Dose modifications of pegylated interferon alpha-2a, as low as 90 µg, were allowed if the patient experienced clinically significant adverse events or laboratory abnormalities. A reduction in the dosage of ribavirin to 600 mg/day was also allowed to manage the occurrence of anemia.

Sample size

Sample size estimation was based on the principal endpoint: SVR proportion (defined as the proportion of patients with an undetectable HCV RNA level 24 weeks after cessation of the antiviral therapy). To identify an increase of 20% in the SVR proportion in the DOT group compared with the non-DOT group, assuming a power of 80% and a two-tailed significance level of 0.05, 97 patients would be needed in each group. Considering a 20% proportion of withdrawals, a total of 244 patients needed to be included.

Statistical methods

The primary analysis population included all patients who received at least one dose of study drug.

Patient characteristics were described using the means and standard deviations for quantitative variables and absolute and relative frequencies for categorical variables. The principal endpoint was the SVR proportion. Follow-up losses were not considered failures for the efficacy analysis. To estimate the effect size, the risk difference and risk ratio were calculated. The same analyses were performed with regard to early virological response (EVR) (i.e., undetectable serum HCV RNA at week 12) and virological response at the end of treatment (ETR). Treatment failure was considered when the reduction of serum HCV RNA at week 12 was <2 log or when serum HCV RNA was detected

at week 24 (for those patients in treatment for 48 weeks), at the end of treatment or 24 weeks after end of treatment.

Subgroup analyses were performed to estimate the SVR with regard to treatment compliance (defined as the number of doses that were actually administered divided by the number of doses that were prescribed) and treatment continuance (defined as the number of days that the treatment was actually administered divided by the number of days that the treatment was prescribed).

The chi-squared test was used to determine whether there were differences in the proportion of SVR between patients with different ranges of treatment duration or different ranges of treatment dose. Chi-squared tests were also used to assess differences in the SVR proportion of patients with different risk factors, such as baseline HIV co-infection, genotype and baseline viral load.

Safety variables (i.e., adverse events and serious adverse events) were summarized using absolute frequencies and percentages per group and compared between both groups by the chi-squared test. The mean levels of liver enzymes at week 12 and at the end of treatment were compared between both groups by a parametric or non-parametric test. The Kolmogorov–Smirnov test was previously used to assess whether the variables were normally distributed. For those variables that followed a normal distribution, the *t*-test was used, and for the ones that did not, the Mann–Whitney test was used.

All analyses were performed using IBM-SPSS Statistics version 18.0 software. The statistical tests were two-sided and considered significant at *p*-value <0.05.

Results

Between July 2006 and April 2007, a total of 257 eligible inmates were identified in the 25 participant prisons. The follow-up ended in September 2008, and the trial was completed in February 2009, as planned. From the initially identified 257 patients, 5 of them were not randomized and 252 were randomized (122 to DOT and 130 to non-DOT) (Fig. 1). For both groups no drug treatment was initiated in 4 patients, and 9 patients who had been randomly allocated to DOT rejected to follow DOT and followed no-DOT (Fig. 1). Therefore, a total 109 patients have been analyzed in the DOT group, and 135 in the non-DOT group (Fig. 1).

Overall, the mean age was 35.9 (SD 6.54), 94.3% were men, 72.1% reported IDU, 21.3% were HIV co-infected and 55.3% had genotype 1 or 4. Most of the patients with genotype 1–4 had mild-moderate fibrosis (93.5% with grade F0–F1–F2). Among patients with genotype G2–G3, the proportion of mild-moderate fibrosis was lower (45.5%). Demographic and baseline clinical characteristics of each group are summarized in Table 1.

Overall median duration of treatment was 33.9 weeks (DOT, 33.9 weeks; no-DOT, 33.4 weeks). Twenty-six patients (10.7%) discontinued study treatment before week 12, and 32 (13.1%) discontinued before the end of treatment. The most frequent reasons for treatment discontinuation were loss to follow-up and treatment failure (Table 2).

The SVR was 63.5%. In the DOT group, SVR was 60.6% (95% CI, 51.17–69.22), and in the non-DOT group, it was 65.9% (95% CI, 57.59–73.38), without a significant

difference between the groups (RR=0.918; 95% CI, 0.746–1.125). Similarly, no significant differences were observed in the secondary efficacy outcomes (i.e., EVR and ETR) between both groups (Table 3).

The mean proportion of administered doses was 97.9% (SD=6.5), without a significant difference between DOT (97.6%; SD=8.1) and non-DOT (98.2; SD=4.9) (*p*=0.117). The mean treatment continuance proportion was 82.9% (SD=30.5), which was also not significantly different between DOT (81.3%; SD=29.6) and non-DOT (84.2%; SD=31.3) (*p*=0.091). The SVR proportion was similar between patients with treatment compliance over 90% and those with treatment compliance less than or equal to 90% (Fig. 2a). SVR proportion was significantly different between patients with different grades of treatment continuance (Fig. 2a). SVR proportions in subgroups of patients with specific risk factors, such as HIV co-infection and viral load, were significantly lower than each complementary subgroup without the risk factor (Fig. 2b). However, no significant differences were observed between intravenous drug users vs. non-users (64.8% vs. 62.1%; *p*=0.702) and methadone users vs. non-users (64.6% vs. 63.0%; *p*=0.817).

Adverse events were reported for 93.4% of the patients (89.7% in the non-DOT group vs. 98.2% in the DOT group, *p*=0.007). Most of the adverse events were mild (82.1%). The most frequent adverse events were anemia (7.1%), thrombocytopenia (5.9%), neutropenia (5.8%) and leucopenia (4.9%). Serious adverse events were reported for 8.2% of the patients (8.1% in the non-DOT group vs. 8.3% in the DOT group, *p*=0.975). There was no unexpected adverse event that had not been previously described in the summary of the product characteristics. Most of the adverse events (85.2%) were solved before the end of the study follow-up. Sixty-eight percent of the adverse events did not require medical intervention and only 9 patients discontinued treatment due to adverse events (Table 2). Levels of ALT and AST decreased over time in both groups, without significant differences between the groups (*p* > 0.05).

Discussion

The proportion of SVR among inmates who underwent standard treatment for HCV infection under direct observation (DOT) was not superior to that achieved by inmates who received the non-DOT standard treatment. Overall, treatment adherence and the SVR proportion were high in both groups.

The lack of difference in the SVR proportion between both groups could be explained by the treatment compliance, which was remarkably high in the overall sample and showed no significant difference between the groups. The fact that in the non-DOT group the only drug that was self-administered was ribavirin could have contributed to the high overall treatment compliance. Moreover, patients in the non-DOT group were given the ribavirin tablets on an on-going basis (one or three times per week), instead of all at once. Similar to our findings, a randomized clinical trial published after the initiation of our study, with the same objective but performed in a different setting (i.e., non-incarcerated patients in a maintenance methadone program), reported no differences between the DOT and the

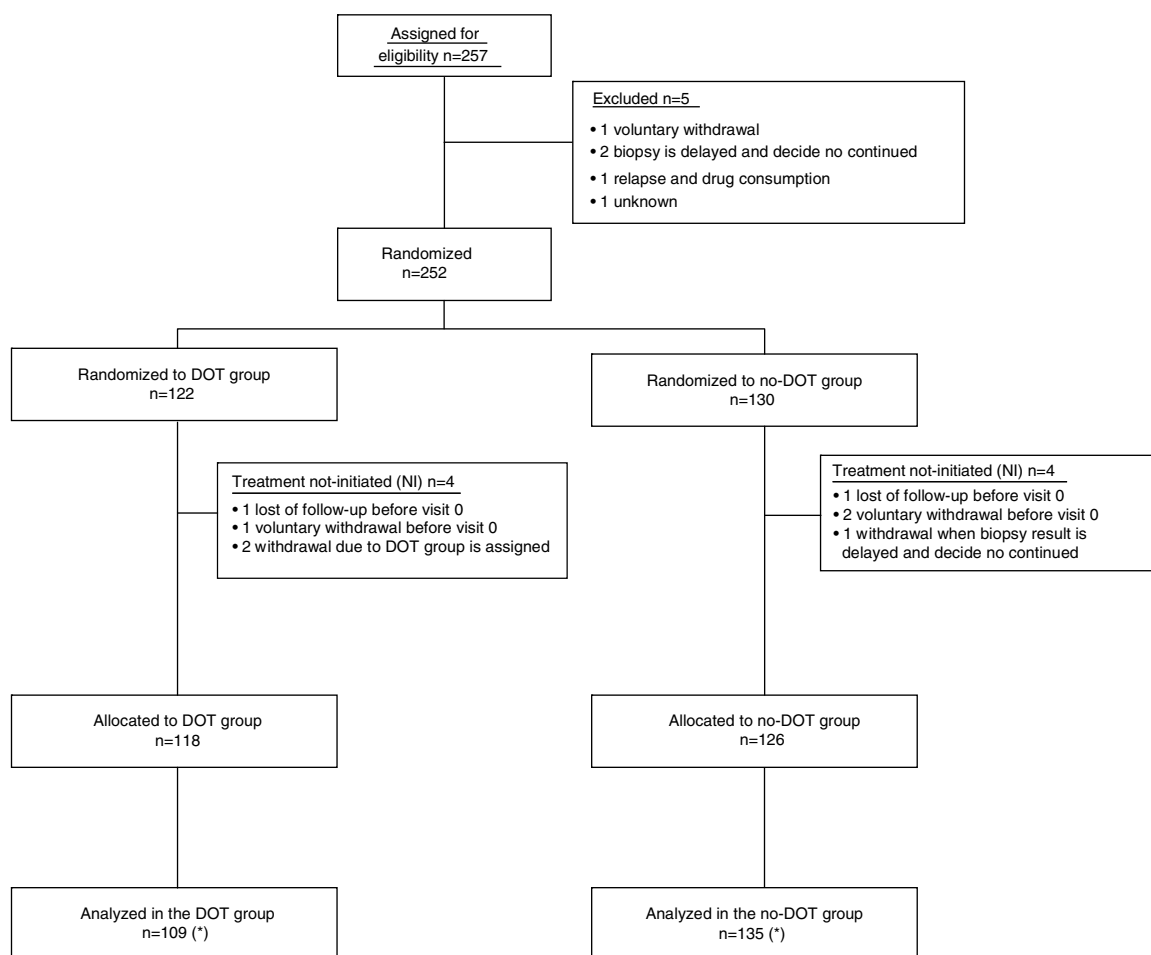


Figure 1 Patient disposition. (*) 9 patients randomized to the DOT group rejected to follow the DOT intervention and were analyzed in the No-DOT group.

non-DOT group.¹⁴ Consistent with our observations, the treatment completion proportion in that trial was also high and was similar between both groups.¹⁴

Although the principal hypothesis of this study was not confirmed, our results show an overall substantial SVR proportion among prison inmates (64%), which is higher than those previously reported in this setting [21–55%]^{15–19} and within the range of the DOT observed for IDU in the outpatient setting [45–98%].^{20–22} Because the previous evidence was based on observational studies, the high SVR proportion observed in this study could be explained by the fact that the study was performed under experimental conditions in a restricted sample of patients with a more favorable risk profile. As expected in this setting, the patients were young, mostly men and showed a substantial proportion of IDU (72%), HIV co-infection (21%) and methadone therapy (32%). However, in general terms, the risk profile, which was typical for prison inmates, was somehow favorable compared with previously reported cohorts in this setting. For instance, the frequency of IDU was lower than those previously reported among inmates with HCV infection in Spain (78–89%), whereas the proportion of patients under methadone maintenance was higher in our cohort.^{4,23} Similarly, the proportion of HIV co-infection (20%) was lower than the proportion reported in a study performed in 18 Spanish

prisons [40%].⁴ The fact that this was a randomized clinical trial explains why some risk factors were less prevalent when compared with previous observational studies. However, given the fact that infectious diseases and treatments can be closely monitored in the prison setting, it should be feasible to obtain in daily clinical practice results that are close to those obtained under ideal circumstances in clinical trials, as it was in an observational study performed in a correctional facility in Canada [66%]²⁴ and a retrospective non-comparative study of inmates who underwent DOT for HCV infection [58%].¹¹

Interestingly, a substantial SVR proportion was also achieved within high-risk subgroups in our trial. For instance, SVR among HIV-co-infected inmates was more frequent (48%) compared with previous cohorts of HIV-co-infected inmates [37%].¹⁵ SVR could have been even higher if weight-based ribavirin dosage had been used. In addition, the SVR proportion achieved among patients with genotypes 1–4 was higher than previously reported in this setting.^{15–17} This finding could be partially explained by the high overall treatment adherence and the high proportion of mild-moderate fibrosis particularly observed in this subgroup. However, as expected, the proportion of SVR was higher among patients with genotypes 2–3 (Fig. 2b).

Table 1 Demographic and baseline characteristics.

	DOT (N=109) ^a	Non-DOT (N=135) ^a	p-Value
Age	36.07 (±6.66)	35.72 (±6.46)	0.683
Male	104 (95.41%)	126.0 (93.33%)	0.487
Weight (kg)	74.30 (±13.11)	74.40 (±11.71)	0.971
BMI (kg/m ²)	24.77 (±3.67)	25.17 (±3.44)	0.391
HIV co-infection	23 (21.10%)	29 (21.48%)	0.942
Abnormally high ALT ^a	85 (77.98%)	104 (77.04%)	0.861
Cirrhosis	1 (0.92%)	2 (1.48%)	0.691
Serum HCV-RNA (>850,000 IU/mL)	44 (40.37%)	58 (42.96%)	0.683
Genotype			0.690
G1	48 (44.04%)	60 (44.44%)	
G2	4 (3.67%)	2 (1.48%)	
G3	44 (40.37%)	59 (43.70%)	
G4	13 (11.93%)	14 (10.37%)	
Fibrosis			0.208
Grade 0	6 (5.50%)	0 (0.00%)	
Grade 1	16 (14.68%)	7 (5.19%)	
Grade 2	3 (2.75%)	2 (1.48%)	
Grade 3	2 (1.83%)	3 (2.22%)	
Grade 4	2 (1.83%)	0 (0.00%)	
Methadone	33 (30.28%)	46 (34.07%)	0.528
On treatment for			
AR	12 (11.01%)	16 (11.85%)	0.837
SSRI	13 (11.93%)	23 (17.04%)	0.263
Other antidepressants	22 (20.18%)	24 (17.78%)	0.633
IDU	80 (73.39%)	96 (71.11%)	0.673

^a N (%) for categorical variables; mean (±standard deviation) for continuous variables.

Table 2 Treatment discontinuation.

	Before week 12 ^a	Before end of treatment ^a
Treatment failure	4 (1.6)	14 (5.7)
Loss to follow-up	9 (3.7)	11 (4.5)
Patient decision	7 (2.9)	4 (1.6)
Adverse event	6 (2.5)	3 (1.2)

^a N (%) out of 244 patients.

Given the high SVR proportion observed even in the high-risk subgroups of our cohort, the overall good SVR results obtained in our study are likely to be explained by the remarkably high treatment compliance, which might also explain why we were unable to observe differences between the two interventions (DOT and non-DOT) or between patients with treatment compliance over 90% compared with those under 90%. In fact, one of the main threats of treatment effectiveness within the prison setting is treatment

discontinuation due to the inmates' release or change of institution.^{15,23} Consistently, in our study we observed that treatment continuance accounted for a substantial fraction of the overall SVR. Therefore, good coordination between institutions should be encouraged to avoid therapy discontinuations due to administrative reasons. This coordination will improve HCV treatment effectiveness within this setting, which in the long run will be beneficial for the community into which inmates are released.

Table 3 Treatment response in each group.

	DOT (N=109)	No DOT (N=135)	p-Value	Risk ratio (95% CI)	Risk difference (95% CI)
SVR	66 (60.6%)	89 (65.9%)	0.386	0.918 (0.746–1.125)	0.054 (–0.075 to 0.182)
EVR	75 (68.8%)	106 (78.5%)	0.085	0.876 (0.747–1.029)	0.097 (–0.021 to 0.212)
ETR	78 (71.6%)	104 (77%)	0.329	0.929 (0.792–1.086)	0.055 (–0.062 to –0.171)

DOT = direct observed therapy; ETR = end of treatment response; EVR = early virological response; SVR = sustained virological response.

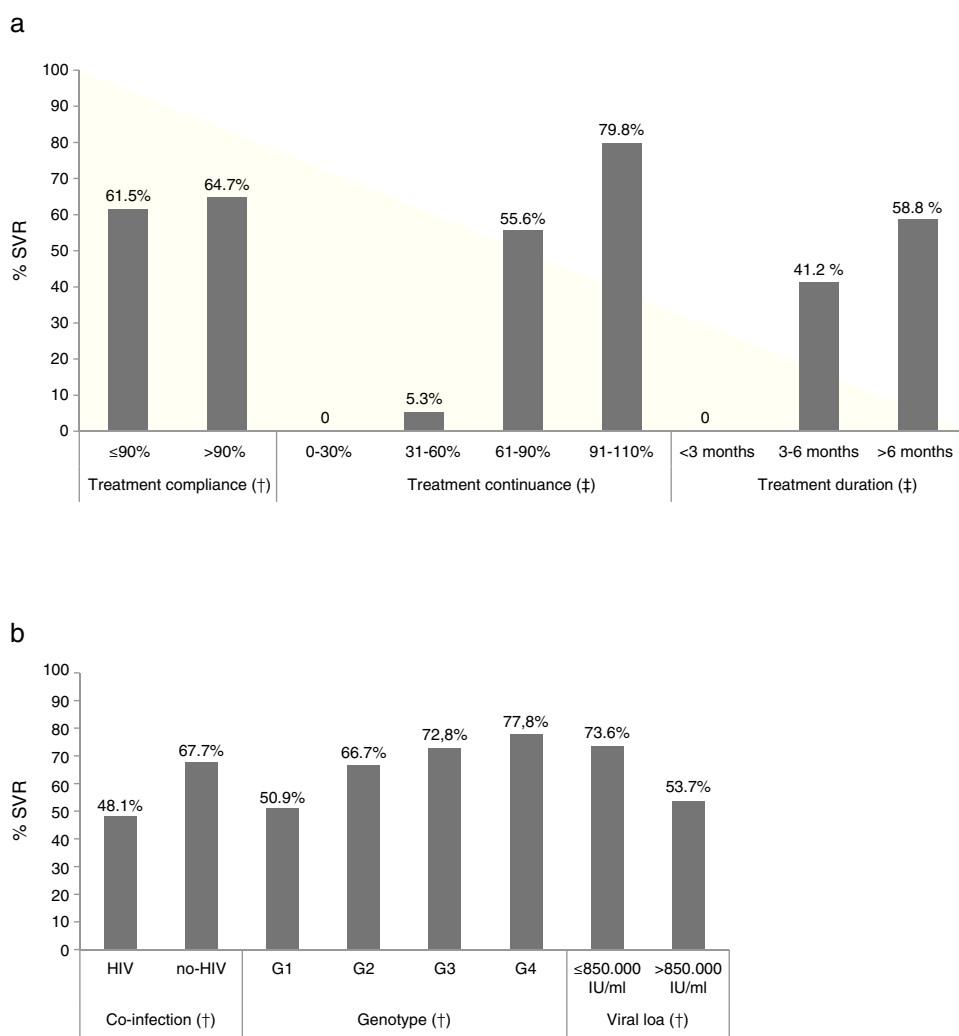


Figure 2 SVR in different subgroups. (a) SVR with regard to treatment compliance and treatment continuance; † $p > 0.05$ (chi-squared test) and ‡ $p < 0.001$ (chi-squared test). (b) SVR with regard to risk factors; † $p < 0.05$ (chi-squared test).

A potential limitation of our analysis could be that we implemented the as-treated principle (i.e., patients were analyzed in the group where they were actually included), instead of following the intention-to-treat principle (i.e., analyzing patients in the group to which they were randomly allocated, regardless the strategy that they finally followed). This may have biased the results in favor of the intervention under study (DOT). However, when the intention-to-treat analysis was undertaken there were no significant differences ($p = 0.27$) between the SVR achieved at the DOT (SVR = 58.4%) and no-DOT group [65.8%],²⁵ consistently to which was obtained in the as-treated analysis. Therefore, we consider that because the potential bias introduced by the 9 patients that crossed-over from the DOT to the no-DOT group would have gone in favor of the DOT group and since no difference in the main outcome (SVR) was observed between groups in both analyses (as-treated and intention-to-treat analyses), the as-treated analysis should not be a matter of concern in this particular case.

To the best of our knowledge, this is the first randomized clinical trial of prison inmates with HCV infection and

the first multicenter clinical study in Spain reporting the SVR proportion achieved with treatment based on ribavirin and pegylated interferon in this setting. Therefore, despite the fact that the principal hypothesis was not confirmed, our results provide evidence on the efficacy of the treatment for HCV infection among prison inmates. The access to health-care professionals, the weekly administration of ribavirin in the no-DOT group and the administration of the interferon by nurses, may have contributed to increase the efficacy in the no-DOT group.

In conclusion, our study failed to demonstrate any additional benefit in terms of efficacy of the direct observed therapy among prison inmates with HCV infection who underwent standard treatment based on pegylated interferon alpha-2a and ribavirin. However, the SVR proportion was remarkably high, possibly due the high proportion of treatment adherence. This latter finding suggests that treatment continuance should be a key target of treatment programs within this setting. The fact that for both strategies the health professionals' intervention was high (i.e., the medication was distributed by nurses in a weekly basis, providing also advice to prevent adverse events) may have

also contributed to the good results obtained and should be considered for treatment programs in other settings.

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Initial data analyses were undertaken by Ignacio Fernández who is employee of Roche Farma S.A.

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Role of the sponsor

The sponsor of the study was the Spanish Society of Prison Health Working Group on Infectious Diseases (GEISEP). GEISEP was involved in the design and conduct of the study, and the preparation, review and approval of the manuscript. The funding organization, Roche Farma S.A., was involved in the conduct of the study, the data management and the analysis of the data, but was not involved in the design of the study and preparation, review and approval of the manuscript.

Conflicts of interest

Dr. Saiz de la Hoya has received fees for lectures and/or consultancy for his participation in advisory boards from Abbott Laboratories, Bristol-Myers Squibb, Boehringer-Ingelheim, Janssen-Cilag, MSD, Roche, Schering Plough and ViiV; Dr. Portilla has received fees for lectures and/or consultancy for his participation in advisory boards from Abbott Laboratories, Bristol-Myers Squibb, Boehringer-Ingelheim, Janssen-Cilag, MSD, Gilead, Roche and ViiV; Dr. Marco has received fees for lectures and/or consultancy for his participation in advisory boards from Abbott Laboratories, Bristol-Myers Squibb, Boehringer-Ingelheim, Janssen-Cilag, MSD, Gilead, Roche and ViiV; Dr. Garcia-Guerrero declares no conflicts of interest; Dr. Faraco has received fees for lectures and/or consultancy for her participation in advisory boards from BMS, Boehringer y Roche; Dr. Anton has received fees for lectures and/or consultancy for his participation in advisory boards, from Bristol-Myers Squibb, Janssen-Cilag, MSD, and Roche; Dr. De Juan has received fees for lectures and/or consultancy for his participation in advisory boards from Roche Pharma; Dr. Pozo declares no conflicts of interest.

Author contributions

All authors have contributed to and agree on the content of the manuscript. The role of each author was as follows:

- Study concept and study design: Saiz de la Hoya P, Portilla J, Marco A, Garcia-Guerrero J, Faraco I, Antón J.
- Data collection: Saiz de la Hoya P, Marco A, Garcia-Guerrero J, Faraco I, Antón J, De Juan J, Pozo E.
- Analysis and interpretation of results: Saiz de la Hoya P, Marco A, Portilla J.

- Preparation of the manuscript drafts: Saiz de la Hoya P, Portilla J, Marco A, Garcia-Guerrero J, Faraco I, Antón J.
- Critical review: all the authors.
- Review and approval of the final version of this manuscript that is being submitted for publication: all the authors.

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