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Effect of hepatitis C antiviral therapy on oral lichen planus and hyposalivation in inmates

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Abstract

Background Oral lichen planus (OLP) and hyposalivation have been reported as extrahepatic manifestations of hepatitis C virus (HCV) infection. Our study evaluated the effect of direct antiviral agents (DAAs) on OLP and hyposalivation in convicts with chronic hepatitis C, examining patients before, during and after the antiviral treatment period with direct acting antiviral agents (DAAs).

Methods We screened 198 inmates for the presence of the HCV antibody. Patients found to be positive underwent a quantitative HCV-RNA test and HCV genotype typing, as well as an oral cavity examination using a scoring system for OLP (REU score) and the clinical oral dryness score (CODS). Subsequently, all patients underwent DAA therapy and a systematic physical examination of the oral cavity at 1, 3 and 6 months from the beginning of treatment.

Results Fifty patients (25.25%) had a positive HCV-RNA test. At baseline, OLP was detected in 4 patients (8%), with a mean REU score of 10.13±4, and different degrees of hyposalivation were seen in 17 patients (34%), with a mean CODS score of 4.71±1.72. Six months after the start of DAA therapy, we observed resolution of OLP in 3 patients (75%) and improvement in the remaining subject with a significantly lower mean REU score (2±4). Hyposalivation disappeared in 5 patients, improved in 10, and remained unchanged in 2 patients with a significantly lower mean CODS score (0.06±0.24).

Conclusion This study demonstrated the effectiveness of DAAs in the treatment of OLP and hyposalivation.

Keywords Direct antiviral agents, hepatitis C virus, oral lichen planus, hyposalivation, prison

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Introduction

Hepatitis C virus (HCV) infection is a widespread disease with a global estimate of 71 million individuals chronically infected [1]. Chronic hepatitis has a progressive evolution and can lead to cirrhosis in 20-30% of infected patients over 20-30 years. Each year, 1-5% of patients with cirrhosis develop hepatocellular carcinoma [2]. Prison represents a confined environment characterized by great exposure and risk of infection [3]. In fact, in prison there are various risk categories, such as patients who inject drugs intravenously (PWID), people living with human immunodeficiency virus (HIV), and men who have sex with men, that increase the risk of HCV infection [4]. The worldwide prevalence of HCV infection recorded within prison is 26% [5]. Within Italian prisons, the prevalence of HCV infection varies from 22-38% [6].

Approximately 74% of individuals with HCV infection develop extrahepatic manifestations, many of which affect the oral cavity [7]. The reported oral lesions are xerostomia, Sjögren's syndrome, sialadenitis, oral lichen planus, bleeding disorders, gingivitis, cheilitis, smooth and atrophic tongue [8].

Oral lichen planus (OLP) is a chronic cell-mediated inflammatory disease of the oral mucosa that typically affects buccal mucosa, tongue and gingiva with bilateral and symmetric

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Conflict of Interest: None

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lesions. There are 6 different forms of lichen: reticular, papular, plaque-like, atrophic/erosive, ulcerative and bullous [9]. The prevalence of OLP ranges from 0.5-2.2% in the general population and develops more frequently between the third and sixth decade of age [10]. The prevalence of OLP in patients with HCV varies from 1.5% in North America and Northern Europe to 1.5-3.5% in Western and Eastern Europe and up to 35% in Egypt, Japan and Southern Europe [11]. Nevertheless, the pathogenic link between HCV and OLP is still not completely understood [12,13].

Xerostomia, or hyposalivation, is the reduction of salivary flow due to alteration of the function of the salivary glands [14]. The prevalence of xerostomia ranges from 12-30%, affecting women more than men [15]. Systemic diseases and local conditions can be the cause of xerostomia [16]. The signs of hyposalivation that can be detected are alterations in ingestion, alterations in taste (dysgeusia), atrophic mucous membranes, halitosis, cervical caries, cheilitis and candidiasis [15,17].

Patients with chronic HCV infection have a prevalence of hyposalivation between 13% and 33%. Early studies by Haddad *et al* have shown the existence of an association between HCV and salivary gland disorders, although this association is still a matter of debate [18-20].

The goal of HCV antiviral therapy is the sustained virological response (SVR), defined as a negative HCV-RNA test 12 weeks after the end of the treatment. The introduction of new direct acting antiviral agents (DAAs), without interferon, allow a high SVR to be achieved with fewer and milder side effects compared to previous therapeutic protocols [21-24].

The aim of our study was to evaluate oral manifestations in patients held in prison, particularly in patients with chronic HCV liver disease, focusing on the evolution of OLP and hyposalivation by examining patients before, during and after the antiviral treatment period with DAAs. There are only a few case reports analyzing the effect of HCV therapy on OLP [25,26], while there is a lack of studies regarding the effect of HCV therapy on hyposalivation.

Patients and methods

We investigated the prevalence of oral lesions in HCV inmates seen at the Health Department of Salerno (C.C. of Fuorni and ICATT of Eboli) from January to August 2019. We screened all 198 inmates for the presence of HCV antibodies (anti-HCV test), of whom 50 (25.25%) tested positive. All subsequently underwent a quantitative HCV-RNA test and HCV genotyping.

HCV-RNA positive patients were selected to begin therapy with DAAs for HCV infection. Therapy consisted of glecaprevir/pibrentasvir (Maviret) and lasted 16 weeks for 2 patients and 8 weeks for the remaining patients. None of them stopped treatment and none ever underwent interferon therapy. Each patient with HCV infection was monitored (HCV-RNA quantitative testing) before the initiation of therapy (baseline), and then 1, 2, 5 or 7 months after starting therapy. At 5 months we evaluated the SVR12 in the patients who underwent the 8-week therapy, while at 7 months we measured the SVR12 in the patients who underwent the 16-week therapy.

Assessment of HCV infection and liver disease

The anti-HCV test was the serum ELISA test (enzyme-linked immunosorbent assay), while the HCV-RNA test used real-time polymerase chain reaction (real-time PCR). The HCV genotype was recorded by PCR. Transient elastography (Fibroscan) was performed in all patients to assess liver fibrosis. In addition, transaminases, platelets, Child-Pugh score, and HIV status were evaluated.

Oral manifestation

In the second phase of the study, all HCV-RNA positive convicts underwent a systematic examination of the oral cavity and perioral soft tissues to identify and record their oral status. The clinic examination was performed before the start of DAA therapy and 1, 2, 3 and 6 months after the start of treatment to monitor the evolution of OLP lesions and hyposalivation. Protocols were observed to reduce the infectious risk linked to the distance of less than one meter between the doctor and the patient. This reduced distance makes the healthcare professional more vulnerable to contact with saliva, blood and other body fluids [27].

OLP

OLP lesions were identified and diagnosed through clinical signs. The severity of OLP lesions was evaluated and monitored based on a semiquantitative scoring system (REU: reticular/hyperkeratotic, erosive/erythematous, ulcerative) developed by Siribang-on Piboonniyom *et al* [28]. The scoring system divides the oral cavity into 10 sites and evaluates the severity of the OLP in relation to the type of lesion in each of the 10 areas. For reticular/hyperkeratotic lesions the score ranges from 0-1 (0 = no white striations, 1 = presence of white striations or keratotic papules); erosive/erythematous areas were scored from 0-3 by area of involvement (0 = no lesion, 1 = lesions less than 1 cm^2, 2 = lesions from 1-3 cm^2, 3 = lesions greater than 3 cm^2); ulcerative lesions were scored from 0-3 by area of involvement (0 = no lesion, 1 = lesions less than 1 cm^2, 2 = lesions from 1-3 cm^2, 3 = lesions greater than 3 cm^2). For each of the 3 types of lesions, a score was derived by summing the scores of all 10 areas: reticular score = $\sum R$, erythema score = $\sum E$, and ulcerative score = $\sum U$ (REU score) with a total score of $\sum R + \sum(E \times 1.5) + \sum(U \times 2.0)$.

Hyposalivation

The evaluation of oral dryness and hyposalivation in patients with HCV infection was based on the clinical oral dryness score (CODS) [17]. The CODS is a 10-point score in which each point is associated with a characteristic sign of oral dryness: 1) mirror sticks to the buccal mucosa; 2) mirror sticks to the tongue; 3) tongue lobulated/fissured; 4) tongue shows loss of papillae; 5) frothy saliva; 6) no saliva pooling on the floor of the mouth; 7) glassy

appearance of other oral mucosa, especially palate; 8) debris on the palate (excluding debris under dentures); 9) altered/smooth gingival architecture; and 10) active or recently restored (last 6 months) cervical caries (>2 teeth). Each sign found has a value of 1 point and the total score corresponds to their sum. The higher the total score, the greater the severity of dry mouth [29].

Statistical analysis

The data are expressed in frequencies and percentages for qualitative variables and as mean ± standard error for quantitative ones, unless otherwise indicated. Significance was expressed at the $P<0.05$ level. When appropriate, a χ^2 test for categorical data and analysis of variance for continuous data were used. Differences in score values at baseline, and after 1, 2, 3 and 6 months were analyzed using the Student's *t*-test. The SPSS for Windows version 15.0 statistical package (SPSS Inc, Chicago, IL, USA) was used for the statistical analysis.

Results

In the first phase of the study, 198 convicts, 22 female, underwent screening for HCV. Table 1 reports the characteristics of the screened patients. There were no differences between the 2 sexes. Fifty patients (25.25%) had a positive HCV-RNA test. Table 2 reports the clinical data of the 50 HCV positive patients. The percentage of genotype 1a was higher in male convicts (41.9% vs. 0%, P=0.02), whereas the percentage of genotype 3a was not significantly higher in females (71.4% vs. 39.5%, P=0.092. HCV viral load was significantly higher in male compared to female convicts (P=0.01). In addition, the Fibroscan score was different between males and females; in female patients there was a higher percentage of F3 score (57.2% vs. 20.9%, P=0.04). Regarding the risk factors, males included a significantly higher percentage of PWID (76.7% vs. 28.65, P<0.001), while sexual promiscuity was mainly recognized in the female population (28.6% vs. 4.7%, P=0.03). All 50 patients underwent therapy with DAAs for HCV infection. There were no side-effects and none stopped the therapy. In 2 patients, F4 on transient elastography, the therapy lasted 16 weeks, while for the remaining patients, who were F0, F1, F2 or F3, the therapy lasted 8 weeks. The treatment was successful in all patients and resulted in negative HCV-RNA even after 1 month from the start of treatment. Laboratory monitoring at 5 months, in the patients who underwent the 8-week therapy, and 7 months, in the patients who underwent the 16-week therapy, revealed negative HCV-RNA in all patients, achieving an SVR12 of 100%. None of the screened patients were under treatment that could influence the course of OLP (e.g., immunosuppressive therapy and/or steroids) or predispose to hyposalivation (e.g., anticholinergics).

Table 1 Demographic and clinical data of screened population

Characteristics	Total N (%)	Males	Females	P-value
Sex	198 (100%)	176 (88.9%)	22 (11.1%)	
Age (years)	41.25±9.7	41.24±9.77	41.36±9.31	0.95
Anti-HIV Ab+	1 (0.5%)	1 (0.6%)	0 (0%)	0.47
Anti-HCV Ab+	50 (25.3%)	43 (24.4%)	7 (31.8%)	0.18
Risk factor				
None	104 (52.5%)	89 (50.6%)	15 (68.2%)	0.125
PWID	76 (38.4%)	71 (40.3%)	5 (22.7%)	0.11
Sex promiscuity	13 (6.6%)	11 (6.3%)	2 (9.1%)	0.61
MSM	5 (2.5%)	5 (2.8%)	N/A	N/A
AST baseline	35.02±17.53	35.49±17.79	31.23±15.19	0.72
ALT baseline	36.84±17.82	36.91±18.17	36.27±15.02	0.65
Platelets	254.95±71.83	255.68±72.94	249.14±63.52	0.25
HBsAg +	(1%)	2 (1.1%)	0 (0%)	0.3
Comorbidities				
None	119 (60.1%)	106 (60.2%)	13 (59.1%)	
Hypertension	17 (8.6%)	19 (10.8%)	2 (9.1%)	0.86
Diabetes	20 (10.1%)	18 (10.2%)	2 (9%)	>0.99
Cardiovascular	6 (3%)	5 (2.9%)	1 (4.5%)	0.28
COPD	17 (8.6%)	16 (9%)	1 (4.5%)	0.90
Dyslipidemia	18 (9.1%)	16 (9%)	1 (4.5%)	0.90
NAFLD	2 (1.1%)	2 (1.1%)	0 (0%)	0.61
IBD	4 (2%)	3 (1.7%)	1 (4.5%)	0.37
Neuro/Psyc	9 (8.5%)	8 (4.5%)	1 (4.5%)	>0.99
Prostatic hypertrophy	2 (1.1%)	2 (1.1%)	N/A	N/A

HIV, human immunodeficiency virus; HCV, hepatitis C virus; PWID, patients who inject drugs intravenously; MSM, men who have sex with men; AST, aspartate aminotransferase; ALT, alanine aminotransferase; COPD, chronic obstructive pulmonary disease; NAFLD, nonalcoholic fatty liver disease; IBD, inflammatory bowel disease; Neuro/Psyc, neuropsychiatric disease

Table 2 Demographic and clinical data of the HCV population

Characteristics	Total N (%)	Males	Females	P-value
Sex	50 (100%)	43 (86%)	7 (14%)	
Age (years)	41.48±11.68	42.05±11.75	38±11.48	0.59
Anti-HIV Ab+	1 (2%)	1 (2.3%)	0 (0%)	0.69
Genotype				
1a	18 (36%)	18 (41.9%)	0 (0%)	0.02
1b	5 (10%)	3 (7%)	2 (28.6%)	0.8
2-3a	2 (4%)	2 (4.7%)	0 (0%)	0.57
4b	22 (44%)	17 (39.5%)	5 (71.4%)	0.092
	3 (6%)	3 (7%)	0 (0%)	0.48
HCV-RNA load	3338586±4448741.78	3777148.84±4650977.93	644557.14±601636.96	0.01
Fibroscan				
F1	0 (0%)	0 (0%)	0 (0%)	N/A
F2	35 (70%)	32 (74.4%)	3 (42.9%)	0.09
F3	13 (26%)	9 (20.9%)	4 (57.1%)	0.04
F4	2 (4%)	2 (4.7%)	0 (0%)	0.57
Risk Factor				
None	8 (16%)	5 (11.6%)	3 (42.9%)	0.2
PWID	35 (70%)	33 (76.7%)	2 (28.65%)	0.009
Sex promiscuity	4 (8%)	2 (4.7)	2 (28.6%)	0.03
MSM	3 (6%)	3 (7%)	N/A	N/A
AST baseline	33.36±15.38	32.47±14.51	38.86±20.42	0.57
ALT baseline	37.58±24.58	37.21±25.56	39.86±18.78	0.66
Platelets	215.20±53.35	214.98±54.37	216.57±50.5	0.65
HBsAg +	0 (0%)	-	-	
Comorbidities				
None	34 (68%)	29 (67,4%)	5 (71.4%)	
Hypertension	5 (10%)	4 (9.3%)	1 (14.3%)	0.69
Diabetes	5 (10%)	5 (11.7%)	0 (0%)	0.57
Cardiovascular	1 (2%)	1 (2.3%)	0 (0%)	0.69
COPD	4 (8%)	3 (7%)	1 (14.3%)	0.51
Dyslipidemia	3 (6%)	4 (9.3%)	0 (0%)	0.48
IBD	1 (2%)	1 (2.3%)	0 (0%)	0.69

HIV, human immunodeficiency virus; HCV, hepatitis C virus; PWID, patients who inject drugs intravenously; MSM, men who have sex with men; AST, aspartate aminotransferase; ALT, alanine aminotransferase; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease

OLP lesions were recognized in 4 (8%) patients and hyposalivation was recognized in 17 patients (34%). No worsening of OLP lesions occurred during DAA therapy. On clinical examination at 1, 2 and 3 months we found improvement in the lesions in all patients. At 6 months the OLP disappeared in 3 patients, while there was an improvement without disappearance in the other one (mean REU score 10.13±4.76 vs. 2±4, P=0.009). At 6 months there was disappearance of hyposalivation in 5 patients (29.4%), improvement in 10 patients (58.8%) and no change in 2 patients (mean CODS 4.71±1.72 vs. 0.06±0.24, P<0.001).

Discussion

HCV infection affects about 26% of the imprisoned people worldwide, while within Italian prisons its prevalence varies from 22-38% [6]. In our study, we enrolled 198 patients and 50 of these tested positive for HCV infection. We found a prevalence of 25.25%, which reflects the conditions in Italian prisons and the presence of people of high risk, such as PWID and those living with HIV. Our study group presented a different prevalence of PWID and sexual promiscuity across gender. In particular, we recognized a higher prevalence of PWID in the male population and greater sexual promiscuity in female inmates, which is consistent with several studies [30,31]. Similarly, our data confirmed the higher prevalence of HCV genotype 1a in the male population, as previously reported [32,33]. All 50 HCV positive inmates underwent antiviral treatment with glecaprevir/pibrentasvir (Maviret), achieving SVR 12 weeks after the end of treatment. These results support the data of some previous studies that reported high efficacy of new DAAs, as well as lower toxicity and with rapid action [21,22]. Furthermore, none of the patients interrupted the treatment nor did any have adverse events typical of IFN, demonstrating the reliability and safety of DAA therapy [23].

From the assessments carried out during the oral screening of HCV-positive inmates, we found 4 cases of OLP, so the percentage of OLP in our study group was 8%. This prevalence differs from the values found in the general population, which range from 0.5-2% [10]. This could be explained by the presence of HCV-positive patients in the sample examined. Indeed, our data are consistent with various studies that have reported a higher risk of OLP in HCV-infected patients than in the non-infected [11]. In the literature it is reported that the eradication of the HCV virus with DAAs results in improvement in extrahepatic conditions, such as cardiovascular, metabolic, renal, hematologic complications [34,35], and lichen planus [26]. Effectively, at the end of DAA treatment we recognized a significant improvement in OLP lesions, with disappearance in 3 cases (75%) and clinical improvement in the remaining one. Our results are consistent with the study by Nagao *et al* [25] which, evaluating 7 patients with HCV-related OLP, demonstrated the disappearance of the lesions in 4 patients and improvement in 3 patients after DAA therapy. Indeed, since we observed improvements in OLP lesions in all DAAs treated patients, we could assume that in these patients the OLP was related to HCV. Furthermore, our findings seem to be consistent with the results of previous studies [36,37] that hypothesized a correlation between HCV and OLP. Conversely, a recent case series and literature review showed persistent or worsened lichen planus in almost 18% of HCV patients under treatment with DAAs, with a better prognosis in patients with only oral manifestations [38]. Further studies are needed to better characterize the effect of DAAs on lichen planus.

The correlation between HCV and hyposalivation is still poorly investigated. We found hyposalivation in 34% of HCV inmates, that is almost 2-fold higher than previously reported [18]; moreover, we described for the first time a significant improvement in hyposalivation in patients treated with DAA. Indeed, there is no evidence regarding changes in hyposalivation in response to DAA therapy in HCV patients. Although the correlation between hyposalivation and HCV has not yet been demonstrated, our clinical experience tends to suggest an improvement in hyposalivation, even if it was not possible to substantiate the diagnosis of hyposalivation with salivary gland biopsy and related blood chemistry tests. Another strength of the present study is that our findings offer a screenshot of the Italian convicted population.

There are some limitations in this study. One is the relatively small sample size and the heterogeneity of patients, which might have limited the generalizability of the findings, especially regarding gender differences. Another limitation is that the design of the study weakens our findings in comparison to results from a prospective longitudinal study, which would be necessary to establish a causal relationship between the improvement in oral lesions and the DAA therapy. Moreover, there were no data about the evolution of oral lesions in non-HCV inmates.

The results of the current study suggest that more regular screening of oral lesions when evaluating HCV-positive inmates might help disclose the presence of OLP and hyposalivation. Furthermore, the study showed an improvement in OLP and hyposalivation in imprisoned patients with HCV infection after therapy with DAAs. Studies conducted on larger samples of patients are needed to confirm that DAA therapy in HCV-infected patients leads to an improvement in HCV-related oral lesions.

Summary Box

What is already known:

- Prison represents a confined environment characterized by great exposure to and risk of hepatitis C virus (HCV) infection
- Oral lichen planus and hyposalivation are extrahepatic manifestation of HCV infection
- The efficacy of HCV direct antiviral agents (DAAs) on oral manifestations of HCV is still under debate

What the new findings are:

- Oral lichen planus and hyposalivation is more common in HCV inmates than in the general population with HCV infection
- DAAs could improve HCV-related oral lichen planus and hyposalivation
- An individual assessment of the oral cavity should be incorporated into regular screening in convicts, especially in those with risk factors

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