Ocular manifestations and treatment safety in hepatitis C patients undergoing direct-acting antiviral therapy: a prospective cohort study*

Manifestações oculares e segurança do tratamento em pacientes com hepatite C submetidos à terapia antiviral de ação direta: um estudo de coorte prospectiva

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ABSTRACT

Objective: To report the frequency of ocular manifestations in patients undergoing direct-acting antiviral therapy and assess treatment safety based on outcomes; to identify demographic variables associated with hepatitis C virus infection; evaluate treatment effectiveness through sustained virological response.

Methods: A prospective cohort study was conducted involving chronic hepatitis C patients undergoing direct-acting antiviral therapy. Ophthalmological evaluations were conducted before treatment initiation and upon completion. Patients were advised to return in case of any visual symptoms.

Results: The study comprised 30 patients, predominantly treated with sofosbuvir + velpatasvir. All patients achieved sustained virological response, and a notable improvement in fibrosis degree post-treatment was observed. No ocular complications attributable to direct-acting antiviral therapy were reported during the study.

Conclusion: This study underscores the safety profile of direct-acting antiviral therapy concerning ocular manifestations. Demographic trends align with existing literature, and all patients achieved sustained virological response alongside improved liver fibrosis. These findings support the efficacy and safety of direct-acting antiviral therapy for hepatitis C patients.

RESUMO

Objetivo: Relatar a frequência das manifestações oculares em pacientes submetidos ao tratamento com antivirais de ação direta e avaliar a segurança do tratamento com base nos resultados; identificar variáveis demográficas associadas à infecção pelo vírus da hepatite HCV; avaliar a eficácia do tratamento por meio da resposta virológica sustentada.

Métodos: Foi realizado um estudo de coorte prospectiva envolvendo pacientes com hepatite C crônica submetidos à terapia com antivirais de ação direta. Foram realizadas avaliações oftalmológicas antes do início do tratamento e após seu término. Os pacientes foram orientados a retornar em caso de qualquer sintoma visual.

Resultados: O estudo incluiu 30 pacientes, tratados predominantemente com sofosbuvir + velpatasvir. Todos os pacientes alcançaram resposta virológica sustentada, e foi observada uma melhora notável no grau de fibrose pós-tratamento. Nenhuma complicação ocular atribuível à terapia com antivirais de ação direta foi relatada durante o estudo.

Conclusão: Este estudo ressalta o perfil de segurança da terapia com antivirais de ação direta em relação às manifestações oculares. As tendências demográficas estão alinhadas com a literatura existente, e todos os pacientes alcançaram resposta virológica sustentada com melhora da fibrose hepática. Esses resultados apoiam a eficácia e segurança da terapia com antivirais de ação direta para pacientes com hepatite C.

INTRODUCTION

According to the *Boletim Epidemiológico – Hepatitis Virais* 2023, from 2000 to 2022, 298,738 confirmed cases of hepatitis C were reported in Brazil.[1] According to estimates, the prevalence of infected people in Brazil (anti-hepatitis C virus [HCV] positive) is approximately 0.7%, which corresponds to approximately 700,000 viremic cases that require treatment.[2]

The primary goal of hepatitis C treatment is to cure the infection, i.e., to achieve a sustained virologic response (SVR) that is defined as undetectable HCV-RNA 12 weeks after treatment ends. Sustained virologic response is generally known to be associated with normalization of liver enzymes, improved fibrosis, and liver function.[3] By achieving this therapeutic target, HCV-related hepatic and extra-hepatic complications, including cirrhosis and hepatocellular carcinoma (HCC), decrease. In addition, it is important to stop the transmission and spread of HCV.

To treat chronic hepatitis C over a long period of time, the therapeutic regimen included interferon (IFN), associated or not with ribavirin (RBV). These drugs caused numerous side effects and had efficacy between 13 and 19% with the use of IFN alone; 31 and 35% with the IFN and RBV combination for 6 months and 38 and 43% with the drug combination for 12 months.[4]

Thus, it is worth noting that almost all patients treated with IFN and RBV have one or more adverse events during their use, which is the main reason for refusal or abandonment of the therapeutic regimen. In the registry studies of IFN alpha-2a and 2b plus RBV, 10 to 14% of patients had to discontinue therapy due to a side effect.[5]

The first report of retinopathy associated with the use of IFN was made in 1990.[6] Subsequently, other researchers reported the presence of cotton wool spots and retinal hemorrhages associated with the use of IFN and RBV, but that this form of retinopathy was relatively mild. The prevalence of these findings in the most diverse studies ranged from 4 to 64%.[7,8] Due to the certain degree of benignity of retinal involvement, ophthalmologic screening is not recommended in patients using these medications.[9]

Isolated cases of decreased or even complete loss of vision following retinal vascular occlusion, optic neuritis, macular edema, or papilledema have been reported during HCV treatment with the use of pegylated IFN.[10]

Vogt-Koyanagi-Harada-like during IFN therapy is another possible rare manifestation affecting HCV patients. The diagnosis is confirmed by retinal fluorescein angiography that shows extra leakage spots, serous retinal detachments, and pigmented epithelial detachments.[11]

Conjunctivitis is the ophthalmologic manifestation most commonly associated with the use of RBV.[12] The association of RBV with IFN increases the risk of retinopathy (50%) compared with IFN monotherapy (14%). Ribavirin therapy alone is not used for the treatment of hepatitis C; therefore, there have been no reports of the ocular effects of RBV alone.[13]

Thus, in 2015, the *Agência Nacional de Vigilância Sanitária* (ANVISA) approved the registration of the first direct-acting antivirals (DAAs) for the treatment of chronic hepatitis C, which would revolutionize the treatment of this pathology, since these drugs were highly effective in studies. This led to the progressive discontinuation of the use of IFN and RBV.

For the treatment of hepatitis C, it is necessary to know the degree of liver impairment or fibrosis that the patient presents. If advanced fibrosis or cirrhosis is detected, the clinical management of the case and the proposed therapeutic regimen will be different in relation to patients with early stages. Staging can be performed through any of the following options: Aspartate aminotransferase to platelet ratio index (APRI), fibrosis-4 (FIB4), liver biopsy or liver elastography. Due to the greater practicality and availability of APRI and FIB4, they end up being the most employed ones.

The Metavir scale is a score used to inform the degree of fibrosis, represented by the letter "F". The classification of the degree of fibrosis is divided into five stages: F0 (represents a healthy liver, which has not suffered any aggression), F1 (liver with minimal fibrosis), F2 (presence of moderate fibrosis, with some septa), F3 (already advanced fibrosis, with numerous septa) and F4 (represents the presence of cirrhosis).[14]

In 2023, as a way of simplifying the stages of diagnosis and treatment of hepatitis C, the Ministry of Health began to recommend the use of pangenotypic medications[15] through the following schemes (Charts 1 and 2).

The safety and efficacy of the DAA-based therapeutic regimen for HCV infection has already been established. There are no reports of serious or lethal side effects associated with these medications. The most commonly reported events were pyrexia and fatigue.[16]

Among the possible ocular manifestations related to these drugs, retinopathy associated with the use of sofosbuvir,[17] non-arteritic anterior ischemic optic neuropathy (NAION) after the use of sofosbuvir + ledipasvir,[18] ocular surface alterations,[19] uveitis,[17,20] and toxic occult retinopathy.[21]

In view of all the above, the disruptive action caused by DAAs in the treatment of hepatitis C is clear; however,

Chart 1. Therapeutic regimen indicated for people over 12 years of age weighing at least 30kg, without previous treatment.

Liver stage	DAA	Dosage	Duration
APRI < 1	Sofosbuvir (SOF) + Daclatasvir (DCV)	1 tablet of SOF+ 1 tablet of CVD, 1x/day	12 weeks
APRI ≥ 1 and without decompensated cirrhosis	Sofosbuvir/ velpatasvir	1 tablet of SOF/VEL, 1x/day	12 weeks
Decompensated cirrhosis	Sofosbuvir/ velpatasvir	1 tablet of SOF/VEL, 1x/day	24 weeks[1]

[1] Ribavirin can be added to the regimen, reducing the duration of treatment to 12 weeks. In patients with decompensated cirrhosis, the initial dose of ribavirin is 500 mg per day, divided into two daily doses, which can be increased depending on patient tolerance. The maximum dose should not exceed 11 mg/kg/day.

Chart 2. Therapeutic regimen indicated for older than 12 years[1] previously treated[2].

Liver stage	DAA	Dosage	Duration
Without cirrhosis or with compensated cirrhosis (Child A)	Sofosbuvir (SOF) + Glecaprevir/pibrentasvir[3]	1 tablet of SOF + 3 tablets of Glecaprevir/ pibrentasvir, 1x/day	12 weeks
Decompensated cirrhosis (Child B or C)	Sofosbuvir/velpatasvir (± ribavirina)[4]	1 tablet of SOF/ VEL, 1x/day	24 weeks

[1] Retreatment regimen consisting of sofosbuvir/velpatasvir can be used in children under 12 years of age with cirrhosis Child B or C, as long as they weigh at least 30 kg.
[2] Previously treated people should be considered those who did not obtain a sustained virological response (SVR) between the 12th and 24th week after the end of treatment. People who have SVR and acquire a new infection (reinfection) should be treated according to Table 1.
[3] For cases with multiple previous failures, ribavirin can be added to the regimen. The daily dose for adults is 1g if weighing <75kg or 1.25g if weighing >75 kg, divided into two daily doses. In these cases, treatment can also be extended to 16 or 24 weeks, according to medical evaluation.
[4] Association of ribavirin at medical discretion. In patients with decompensated cirrhosis, the initial dose of ribavirin is 500 mg per day, divided into two daily doses, which can be increased according to patient tolerance. The maximum dose should not exceed 11mg/kg/day.

there are few studies in the literature evaluating the safety of these medications in terms of ophthalmological aspects. This fact justified and motivated us to carry out the present research.

The objectives of this study were: to report the frequency of ocular manifestations in patients undergoing direct-acting antiviral therapy and assess treatment safety based on outcomes; to identify demographic variables associated with hepatitis C virus infection; and to evaluate treatment effectiveness through sustained virological response.

METHODS

This is a prospective study aimed at reporting the frequency of ophthalmologic manifestations in patients with chronic hepatitis C undergoing treatment with DAA, with a confirmed diagnosis of hepatitis C through two laboratory tests, anti-HCV and HCV-RNA. The patients included in the study were referred by the Hepatology Outpatient Clinic and followed up at the Department of Ophthalmology, between March 2022 and July 2023. The patients were divided into groups according to the medication being used.

Patients with chronic hepatitis C with a confirmed laboratory diagnosis (anti-HCV and HCV-RNA reagents), who underwent treatment with the use of DAA for 12 or 24 weeks and who agreed to participate in the research by signing the Free and Informed Consent Form participated in the study.

Patients with retinopathy patients with glaucoma; patients with a history of uveitis; patients using IFN or RBV; individuals co-infected with other sexually transmitted infections; presence of clinically decompensated chronic diseases that may present ocular manifestations, such as: systemic arterial hypertension, diabetes mellitus, and autoimmune diseases.

The ophthalmologic evaluation was always performed by the same ophthalmologist. The evaluations began with a detailed ophthalmologic anamnesis, consisting of the main complaint, history of the current disease, previous pathological history, ophthalmologic history, social history, and family history.

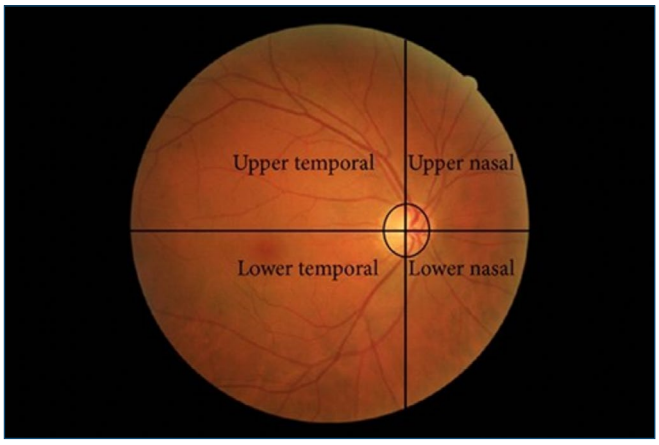
The following data were collected and later entered into a Microsoft Office Excel 2019 spreadsheet: age, gender, probable source or mechanism of exposure, degree of fibrosis, type of DAA, and duration of treatment. The genotype was not evaluated due to the fact that genotyping research was considered unnecessary by the Ministry of Health.

The patients were evaluated at two different periods: before the beginning of the proposed treatment regimen and at the end. All patients were instructed to return before the period if they presented any visual signs or symptoms, but none of the patients complained during the use of the medications.

The ophthalmologic physical examination consisted of the following steps, respectively: measurement of corrected visual acuity through refraction (using the ETDRS table), examination of the pupils under penumbra to evaluate direct and consensual photomotor reflexes, biomicroscopy of the anterior segment, applanation tonometry, and fundoscopy under mydriasis.

To better organize fundoscopy, the retina was divided into four quadrants (superior temporal, inferior temporal, superior nasal, and inferior nasal) by imaginary lines, one horizontal and one vertical passing through the optic disc, as shown in figure 1.

Initially, the descriptive analysis of the data was performed in a spreadsheet of the Microsoft Office Excel Plus 2019 program, in which the tables were inserted. Then, the proportions and frequencies for the categorical variables, as well as the means and medians, were obtained.



Source: Calvo-Maroto et al.[22]

Figure 1. Illustrative photo of the retinal quadrants.

To test the normality of the data, the Shapiro-Wilk test was used and the correlation between the variables was later performed. With a p-value < 0.05 in all samples, the hypothesis of normality was rejected, and the Spearman test was performed.

The data were categorized, stored, and statistically analyzed using the Jamovi statistical software. The level of statistical significance for all analyses was set at 0.05.

The present study was approved by the Research Ethics Committee of the Hospital Universitário Gaffrée e Guinle (CAAE: 52740721.7.0000.5258), with approval number 5,261,481, dated February 24, 2022.

RESULTS

The sample consisted of 30 patients. Of these, 16 (53.4%) were male, and 14 (46.6%) were female; 26 patients were treated with sofosbuvir + velpatasvir (86.6%), 3 with sofosbuvir + ledispavir (10%) and only 1 with glecaprevir + pibrentasvir (3.3%). Regarding the mechanism of exposure, 20 patients (66.66%) did not know the probable source (unknown or community). Among the patients with a known source of contamination, blood transfusion prevailed in six cases (20%), followed by sexual intercourse in three (10%) and use of injectable illicit drugs in one (3.3%). The median age of the patients was 61 years old (interquartile range [IQR]52 - 66). The demographic characteristics of the study participants are shown in table 1.

The degree of fibrosis based on non-invasive methods (Apri, FIB4 or hepatic elastography) of the patients was stratified based on the Metavir scale. Table 2 shows the number of patients classified in each stage of fibrosis, before and after treatment.

Spearman's correlation was used to evaluate the significance of the improvement in the degree of fibrosis before and after treatment with DAA. The result of the correlation was 0.855 (p-value<0.001), which represents a strong correlation[23] (Figure 3).

The mean visual acuity in log MAR before treatment was 0.036 in the right eye and 0.05 in the left eye. None of the patients presented alterations in visual acuity during and after treatment.

During the study period, no patient had ocular complications related to the use of DAA. Importantly, all study participants achieved SVR.

Table 1. Demographic characteristics of the study participants

Patient	Sex	Age	Exposure mechanism
1	Female	58	Unknown
2	Female	65	Unknown
3	Female	77	Transfusional
4	Female	63	Unknown
5	Male	58	Unknown
6	Female	61	Unknown
7	Female	52	Unknown
8	Female	58	Transfusional
9	Male	57	Unknown
10	Male	40	Unknown
11	Male	71	Unknown
12	Male	61	Transfusional
13	Male	64	Sexual
14	Male	70	Unknown
15	Female	71	Unknown
16	Male	64	Transfusional
17	Female	42	Unknown
18	Female	43	Unknown
19	Female	66	Transfusional
20	Female	58	Unknown
21	Female	58	Unknown
22	Male	52	Sexual
23	Male	66	Drugs
24	Male	45	Unknown
25	Male	46	Sexual
26	Male	44	Unknown
27	Male	73	Transfusional
28	Male	63	Unknown
29	Female	65	Unknown
30	Male	67	Unknown

Table 2. Degree of fibrosis before and after treatment

Degree of fibrosis	Before treatment (number of patients)	After treatment (number of patients)
F0	2	9
F1	8	16
F2	11	3
F3	4	1
F4	5	1

DISCUSSION

Identified in 1989, the hepatitis C virus represents one of the most relevant public health problems today. It is one of the leading causes of acute and chronic hepatitis in the world.[24] Its natural history of asymptomatic evolution contributes to the large number of unaware carriers, in

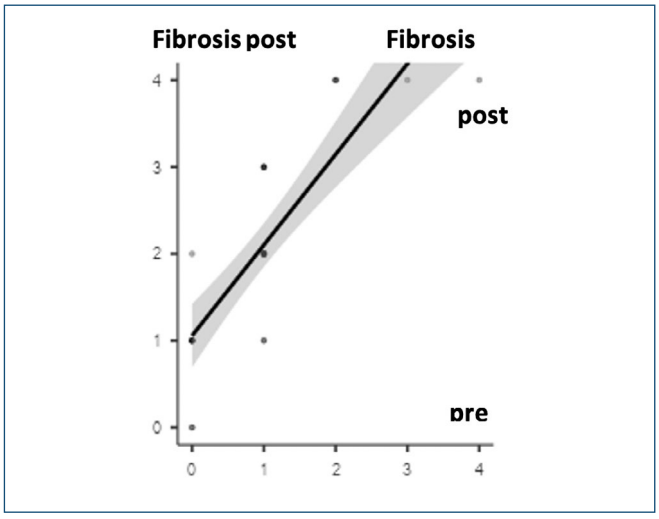


Figure 3. Correlation between degree of fibrosis pre-and-post-treatment.

many cases the diagnosis being made only after the development of severe complications, such as liver cirrhosis and HCC. In addition, its enormous capacity to become chronic in up to 85% of those infected also constitutes a negative highlight.

Analyzing the epidemiology of hepatitis C in Brazil since 2000, it can be inferred that most cases occurred in males (57.4%), which is in line with the present study, in which 53.4% of the patients were male.

Regarding the probable source or mechanism of exposure, it is noteworthy that 20 patients (66.66%) did not know the probable source, six cases (20%) were related to previous blood transfusion, sexual access was attributed to three patients (10%), and injectable illicit drugs were used in only one case (3.3%). Compared to the 2023 *Epidemiological Bulletin on Viral Hepatitis* (Ministry of Health), the percentage of unknown sources is close to the national average (58.8%). However, in the study in question, blood transfusion predominated as the known cause, unlike the bulletin, which places the use of injectable illicit drugs as the most prevalent.

Considering the age groups, between 2000 and 2022, it is observed that the highest percentage of reported cases of hepatitis C occurred in the age group above 60 years. This finding is corroborated by the present study, since the median age of the patients was 61 years (IQR 52-66).

Before treatment, 15 patients (50%) had moderate or advanced fibrosis and 5 (16.6%) were classified as cirrhotic, based on the Metavir scale. After antiviral treatment, these numbers decreased to 4 (13.33%) and 1 (3.33%), respectively. The improvement of fibrosis after treatment with DAA has been reported by several studies.[25]

Spearman's correlation demonstrated the strong significance of the improvement in the degree of fibrosis after treatment, with a result of 0.855 (p-value<0.001).[23]

Chin-Loy et al. reported a case of retinopathy and bilateral non-granulomatous anterior uveitis in a patient using sofosbuvir and RBV.[17] However, it should be noted that the patient in question had positive rheumatoid factor and antinuclear factor, which may explain the uveitis in question. In addition, the association of RBV with IFN increases the risk of retinopathy (50%) compared with IFN monotherapy (14%), which may suggest the association of RBV with retinopathy. However, since RBV alone is not used for the treatment of hepatitis C, there is a lack of studies to confirm this hypothesis.[13]

Salman conducted a study with 300 patients, dividing them according to the treatment regimen into two groups: peginterferon + RBV plus sofosbuvir; and peginterferon + RBV. At the end of their evaluation, it was shown that the group using sofosbuvir had a dysfunction of the tear film during the treatment. It should be noted that peginterferon and RBV can promote the occurrence of dry eye by inducing inflammation, autoimmune changes in the lacrimal gland and ocular surface. A larger-scale study with longer follow-up is needed to better assess how new DAA can alter the ocular surface.

Manoharan et al. reported a case of NAION in a patient after the use of sofosbuvir + ledipasvir associated with RBV for 24 weeks.[18] To date, this is the only reported case of this neuropathy with possible association with DAA. The pathogenesis of NAION is still uncertain, and clinical diagnosis may encompass several distinct sources, including thromboembolism, systemic hypotension, and atherosclerotic vascular occlusion. However, in most cases no underlying cause is found, so it is occasionally referred to as "idiopathic".[26]

Padidam et al. reported the presence of posterior uveitis in six patients using sofosbuvir + ledipasvir.[20] One of the patients had a history of chronic uveitis and another had inflammation soon after cataract surgery.

Massengill et al. reported a case of loss of acuity and visual field in a patient shortly after initiation of glecaprevir + pibrentasvir without a defined cause, through ophthalmologic examination and multimodality (optical coherence tomography and autofluorescence).[21] Inflammatory, infectious, nutritional, and genetic screenings were also negative. Only the electroretinogram was able to detect a decrease in the responses of cones and rods. Thus, the hypothesis of toxic occult retinopathy related to medication was raised.

This study presents results similar to those found by Abd Elaziz et al.[27], who followed the treatment of 200 patients using sofosbuvir + daclatasvir, without any of them presenting ocular manifestations.

Taking into account the possible association between the medications and the uveitis found, there is still no correlation between the reported cases, since Chin-Loy et al. described anterior uveitis and Padidam et al. reported posterior uveitis.[17,20] Some studies have used DAA in association with RBV,[17,19] a drug whose possible isolated ocular effects are not yet fully understood.[13] Other authors, reported isolated cases with an unconfirmed causal association, such as Manoharan et al.[18] and Massengill et al.[21]

Thus, there are few studies available on ocular manifestations associated with DAA. Further studies are needed, with a larger number of patients and longer observation time to confirm the safety of these medications in terms of ophthalmologic aspects of patients.

CONCLUSION

None of the patients had ocular manifestations related to direct-acting antivirals during their use, which corroborates the safety of these drugs in terms of ophthalmologic aspects.

The epidemiological data of the study regarding age, sex, and mechanism of exposure are similar to those reported by the Ministry of Health in 2023.

All patients had a sustained virologic response at the end of treatment. In addition, the improvement in the degree of hepatic fibrosis in the group studied should be highlighted.

AUTHOR CONTRIBUTION

Carvalho GT contributed to the conception and design of the study, analysis and interpretation of the results, writing and critical review of the manuscript content. Mello CEB, Simões KMP, and Medina FMC contributed to the analysis and interpretation of data and critical review of the manuscript content. Motta MMS, Fakoury MK, Coimbra BV and Melo LGN contributed to the conception and design of the study and critical review of the manuscript content. All authors approved the final version of the manuscript and are responsible for all aspects of it, including ensuring its accuracy and integrity.

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