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REVIEW ARTICLE

An eye on hepatitis C: a review

O olho na hepatite C: uma revisão

Romero Henrique Carvalho Bertrand[1], Adriana Leite Xavier Bertrand[2], Thais Mota Gomes[3], Adalgisa de Sousa Paiva Ferreira[4]

1. Departamento de Medicina II, Universidade Federal do Maranhão, São Luís, MA, Brazil.
2. Departamento de Oftalmologia, Centro de Ensino Unificado do Maranhão, São Luís, MA, Brazil.
3. Universidade Federal do Maranhão, São Luís, MA, Brazil.
4. Departamento de Medicina I, Universidade Federal do Maranhão, São Luís, MA, Brazil.

ABSTRACT | This review aims to caution ophthalmologists about the ocular consequences leading to the diagnosis of hepatitis C virus infection. In addition, in this context, the effects of old and new drugs are discussed in the ophthalmological setting. The importance of early diagnosis and the curative treatment of the disease has been reported in the national and international literature, demonstrating that its progression has important implications for daily clinical and surgical ophthalmological practice. Despite the scarcity of studies on new direct-acting antiviral drugs, fewer side effects of these drugs have been shown when compared with conventional interferon treatment with or without ribavirin. The ophthalmologist's risk of becoming infected, as demonstrated by the presence of the virus in ocular structures, and the possibility of contamination, is also discussed.

Keywords: Hepatitis C/ complications; Hepatitis C/drug therapy; Interferon/therapeutic use; Direct-acting antiviral drugs

RESUMO | Esta revisão objetiva alertar os oftalmologistas sobre as consequências oculares que levam ao diagnóstico da infecção pelo vírus da Hepatite C. Além disso, neste contexto, os efeitos de drogas antigas e novas são discutidos no cenário oftalmológico. A importância do diagnóstico precoce e do tratamento curativo da doença tem sido relatada na literatura nacional e internacional, demonstrando que sua progressão tem implicações importantes para a prática oftalmológica diária. Apesar da escassez de estudos sobre novos medicamentos antivirais de ação direta, foram demonstrados menos efeitos colaterais desses medicamentos quando comparados ao tratamento convencional com interferon, com ou sem ribavirina associado ou não à rivabirina. O risco do oftalmologista de se infectar, como demonstrado pela presença do vírus nas estruturas oculares, e a possibilidade de contaminação, também é discutido.

Descritores: Hepatite C/complicações; Hepatite C/tratamento farmacológico; Interferon/uso terapêutico; Drogas antivirais de ação direta

INTRODUCTION

Hepatitis C virus (HCV) infection is a public health problem and one of the most common infections in humans. The HCV has a heterogeneous global prevalence, with areas of low, intermediate, and high predominance[1]. Between 2% and 3% of the world's population is estimated to be carriers of the virus, corresponding to 123-180 million infected people[2].

A population-based study in Brazil involving only the state capitals demonstrated that the prevalence of infection varied between regions: North, 2.1%; Northeast, 0.7%; Central West, 1.3%; Southeast, 1.3%; South, 1.2%; and Federal District, 0.8%[3].

HCV transmission is primarily parenteral. In the past, the primary sources of transmission were transfusions of blood and blood products before the virus was identified[4]. The incidence of the disease has declined steeply in recent years because transmission by blood and blood products is regulated in the vast majority of countries[5].

Despite the control of blood products, other mechanisms of transmission still remain[6]. Geographical differences in risk factors exist for new notified cases. While unsafe practices among intravenous drug users constitute the primary mechanism of transmission in the U.S. and most industrialized countries[6], invasive procedures by health services have become the most important risk factors in other regions of the world[7,8].

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Corresponding author: Romero Henrique Carvalho Bertrand

Rua Parnaíba, nº 01/1400 - Condomínio Casa do Morro - São Luis - MA - 65075-839 Brazil - E-mail: romerobertrand@uol.com.br

Other less frequently reported mechanisms are occupational exposure, vertical transmission, and sexual contact with carriers of the virus[9]. A national survey coordinated by the Brazilian Society of Hepatology revealed that hospital procedures are the primary risk factors for new HCV infections[10].

Acute infection resolves spontaneously in 20-40% of cases, while the remaining infected individuals are chronic carriers of the HCV[11]. The risk of liver cirrhosis among chronic carriers is between 15% and 30% within 20-30 years. Cirrhosis and its complications, such as HCV-associated hepatocellular carcinoma (HCC), constitute approximately 700,000 deaths per year worldwide[12].

The current treatment for hepatitis C, which utilizes direct-acting antivirals (DAAs), cures the infection in >90% of patients, halting the progression of liver disease and significantly reducing the development of HCC[13].

HCV infection is often asymptomatic until the onset of complications of liver cirrhosis[14]. Symptoms include extrahepatic manifestations associated with HCV, including cryoglobulinemia, salivary gland dysfunction, glomerulonephritis, thyroiditis, skin disorders, pulmonary fibrosis, Behçet disease, polyarthritis, fibromyalgia, Guillain-Barré syndrome, thrombocytopenic purpura, ocular disorders, and other less common conditions[15-19]. Such manifestations should prompt the physician to screen for the presence of the HCV because diagnosis of the infection and the currently available treatment may cure the infection, thereby preventing progression to cirrhosis and its associated complications.This review updates the reader about the magnitude of the problem and the implications for daily clinical and surgical ophthalmological practice.

Ophthalmologic changes associated with the HCV

Several disorders have been associated with chronic HCV infection. The primary site of ocular manifestation of the disease is the ocular surface, and the most common finding is keratoconjunctivitis sicca[20-23]. Several studies have reported a high frequency of dry eye syndrome[24,25] associated or not with Sjögren syndrome (SS) when compared with the general population[26-30]. Other ocular manifestations have been documented, including keratitis, scleritis, and retinopathies[31,32].

The pathogenesis of ocular changes is possibly due to the direct action of the virus and immunological reactions to certain viral antigens and even immune complexes[33-35]. The same explanation could apply to other HCV-associated extrahepatic manifestations, of which cryoglobulinemia is one of the more frequent manifestations, found in up to 50% of HCV carriers and most frequently presents as vasculitis in various organs[33-36]. The virus could also act as a trigger for autoimmune reactions, causing tissue damage and dysfunction[37]. These alterations could also enable a pathologic manifestation in the posterior pole of the eye, such as retinopathy, papillitis, and neuritis[38,39].

Ocular surface

Ocular surface alterations have been described in the literature for >20 years. Haddad et al. demonstrated alterations in 57% of patients with HCV (16 of 28 patients) versus 5% (1 of 20 patients) of controls[24]. Pawlotsky et al. also observed a higher frequency of such alterations in patients with HCV (14%) than in controls (0%)[40]. Similarly, Jorgensen et al. reported dry eyes in 19% of patients in a sample of HCV carriers[20]. In addition, Leyland et al. investigated whether chronic hepatitis C was associated with ocular disease in 25 patients with HCV, based on disease history assessment, the dry eye evaluation questionnaire, and the tear film break-up test (break-up time [BUT]). The results indicated changes in 44% of patients with a high incidence of altered BUT (≤10 seconds)[41]. The associated salivary gland involvement with histological confirmation of SS has been linked to HCV[34]. Verbaan et al. also evaluated salivary and ocular involvement among patients with HCV, observing that 67% of patients had at least 1 abnormal objective test indicative of keratoconjunctivitis or xerostomia, while 38% demonstrated lacrimal and salivary gland involvement[26]. Later, Cacoub et al. reported on 321 patients with HCV of whom 10% had dry mouth or dry eye[23].

Recently, a more detailed study by Gumus et al. reported a higher frequency of changes in all Ocular Surface Disease Index (OSDI, Schirmer I, Schirmer II, and BUT) scores in patients with chronic hepatitis C than in noninfected individuals in an age- and sex-matched sample[42].

Recently, 2 studies conducted in Brazil also emphasized the predominance of ocular surface alterations. Gomes et al. detected ocular surface disease in at least 1 eye in 88% of infected patients, exhibiting alterations in assessment parameters such as rose bengal staining (a vital dye that evaluates live epithelial cells without tear film protection) and the BUT test, in addition to observing altered stoichiometry (a test that evaluates corneal sensitivity) and less sensory perception in the eyes of infected patients[43]. In a study of 138 infected patients versus controls, Zeni et al. found altered BUT and Schirmer test results and observed higher mean tonometry values in the infected group[44].

The pathogenesis of dry eye in patients with HCV infection involves the destruction of glandular cells, possibly by antigenic reactions to immunocomplexes produced by viral antigens and specific antibodies or by the direct action of the virus[32,42]. Other possibilities suggest that lymphocytic infiltration of the lacrimal gland[45,46] or modification of corneal sensitivity occurs due to sensory alterations in the trigeminal nerve, reducing tear production[43].

Another ocular surface alteration associated with HCV infection is the presence of peripheral corneal ulceration, the so-called Mooren's ulcer[44]. Wenkel, Krist, and Korn identified the HCV in the tears of infected individuals. The proposed mechanism suggests that the peripheral cornea is affected by the presence of elevated immunoglobulin M, macrophage counts, Langerhans cell counts, and complement C1 fraction associated with high concentrations of HCV-RNA in tears and aqueous humor. Antigen-antibody complexes formed in the cornea near the limbal vessels or carried by tears trigger a chain of inflammatory reactions, especially in the peripheral cornea. In addition, immune complex deposition in the limbus causes immune vasculitis[47].

The direct association of Mooren's ulcer with HCV was challenged in studies by Wang et al. and Jain et al., who analyzed 50 patients positive for HCV for signs of keratitis, but found no such association[48,49]; and Zegans et al. obtained the same result in 21 patients[19]. However, the clinical improvement of Mooren's ulcer during treatment for hepatitis C, as observed by Erdem et al., suggests an association between the 2 conditions[50].

The association between hepatitis C and keratitis is controversial; however, most researchers suggest that patients without rheumatologic disease, but with significant inflammatory reaction in the peripheral region of the cornea be screened for HCV infection[44,49,51].

HCV and the retina

Clinical studies have shown that retinopathies are associated with HCV[52]. In their study, Abe et al. reported retinopathy in 31.8% of 85 cases versus 6% of 100 controls. Alterations included retinal hemorrhage, both in the posterior pole and in the retinal periphery, in addition to cotton wool spots. Such alterations have been attributed to ischemia, which could be associated with infection-induced systemic vasculitis, phenomena similar to those occurring in diabetic retinopathy[45,53,54], and intra-arterial obstruction due to embolization caused by leukoaggregates as a result of complement activation[55], a mechanism also associated with the development of Purtscher-like retinopathy in patients with chronic HCV infection as demonstrated by peripapillary cotton wool spots and retinal pallor superficial to the macula[56].

HCV and its associations with tumors of the eye and its adnexa

The association between hepatic cirrhosis as a result of the HCV and HCC is well established[57,58] and attributed to both cirrhosis and the associated presence of the HCV as a carcinogen. The association between non-Hodgkin lymphoma and the HCV is described in previous studies[59,60]. Some ocular and orbital tumors, such as lacrimal gland lymphoma[61] and rare tumors such as orbital plasmacytoma, are reported to be associated with the HCV[62]. Extranodal marginal zone lymphoma of MALT-type (MALT lymphoma), the subtype found most commonly in ocular adnexal lymphoma, is also associated with HCV infection[63].

Ocular changes related to HCV treatment

Hepatitis C treatment has utilized various strategies over the past 30 years. The primary strategies involved the use of interferon (IFN) combined with ribavirin, achieving cure rates of approximately 50%, but with many side effects[64]. In 2011, the first generation of DAAs was in use, but still in combination with IFN, with cure rates of approximately 80%[65,66]. However, despite the increased sustained virologic response, the severe side effects, especially with advanced disease, led to replacing this therapy with second-generation IFN-free DAAs in 2013, reaching virologic response rates of >90% without significant side effects[67].

The drugs daclatasvir, sofosbuvir, simeprevir, dasabuvir, paritaprevir, ledipasvir, and ombitasvir, all DAAs, were included in the list of essential medicines of the World Health Organization (WHO) in 2015, and their use is regulated by the updated 2016 WHO *Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection*[1].

Ocular changes associated with IFN and ribavirin treatment

Despite all the advances in the treatment of hepatitis C and the recommendation by the main WHO Guidelines for the preferential use of DAAs[65,66,68], IFN is still part of the treatment regimens used in some regions of the world[69,70]. IFN, an immunomodulatory cytokine, is produced naturally by lymphocytes in response to viral

infections[71], and when administered subcutaneously, it inhibits HCV replication and modulates the immune response against infected liver cells[72].

The HCV treatment regimen recommended by Brazil's Ministry of Health involves the use of DAAs. However, depending on the HCV genotype/subtype, some regimens still use IFN in its pegylated form (PEG-INF). In addition, recommendations by the European Association for the Study of the Liver justified the acceptance of PEG-INF by the heterogeneity of income per capita and health insurance systems throughout Europe and elsewhere. The high cost of new therapies is one of the primary barriers to their implementation[73].

Despite all the changes in hepatitis C treatment, ocular alterations triggered by using IFN with or without ribavirin are reported in many past and current studies[74,75].

The incidence of IFN-associated retinopathy is variable, occurring in 18-86% of patients. For instance, Lima showed retinal changes in 35.7% (10 of 28) of patients receiving INF and in 33.3% (8 of 24) of those receiving PEG-INF[76]. The deposition of immune complexes associated with lymphocyte infiltration in the retinal microcirculation may be responsible for microvascular occlusion and focal ischemia[77].

In addition to retinopathies, other alterations of the ocular posterior pole have been documented as related to HCV treatment, including macular edema, unilateral ischemic neuropathy, and bilateral anterior ischemic optic neuropathy, with blindness and choroidal and optic nerve infarction associated with polyarteritis nodosa[28,78]. Vogt-Koyanagi-Harada (VKH) syndrome and panuveitis are also described in patients during IFN treatment[21,79]. The diagnosis of VKH is confirmed by retinal fluorescein angiography, typically showing multiple dots in the retinal pigment epithelium, and bilateral serous retinopathy and serous retinal detachment in combination with papillitis and optic disc edema[80].

Conjunctivitis is the primary ocular side effect of ribavirin. In addition, ribavirin increases the risk and severity of retinopathy when combined with IFN[81]. This potentiating effect of IFN can be ascribed to changes in the immune system in the balance between type 1 and 2 T-helper cells[82,83].

It is well known that patients undergoing IFN treatment with or without ribavirin may develop ocular diseases, including asymptomatic ones. And as no epidemiological studies have described the incidence of these pathologies, such patients should be examined and monitored, particularly in the event of complaints or adverse events[84]. Tsolakos et al. suggest that patients with pre-existing retinopathy, especially patients with hypertension and diabetes, should be monitored monthly during the course of hepatitis C treatment[74,85,86]. Recommended eye examinations include visual acuity, slit-lamp biomicroscopy, and ophthalmoscopy[87].

Ocular changes associated with DAA treatment

There are few available studies on the side effects of new treatments for hepatitis C, especially in the ophthalmologic context.

A recent case report by Chin-Loy et al. provided the first description of retinopathy and uveitis associated with the use of ribavirin and sofosbuvir[88]. Physical examination findings included conjunctival injection, fine keratic precipitates, bilateral flare, and the presence of peripapillary cotton wool spots. The pathogenic mechanism has not been elucidated, but the authors believe that the ocular alterations are related more to the use of sofosbuvir as the decreased dose of ribavirin did not stop disease progression. Moreover, a synergistic action of sofosbuvir and ribavirin may be possible as demonstrated when the latter is combined with IFN[88]. Salman performed subjective (OSDI) and objective tests (Schirmer tests, BUT, and nucleus-to-cytoplasmic ratio analysis of conjunctival cells by cytology) in 150 patients treated with sofosbuvir + PEG-IFN/ribavirin (group 1) compared with 150 patients treated with PEG-IFN/ribavirin alone (group 2). The results demonstrated a significant difference in the tests performed before and during the treatment of patients in group 1 and between groups 1 and 2 during treatment, indicating greater ocular surface involvement and the development of dry eye in subjects treated with sofosbuvir[89].

Perello et al. published a case series comparing a group of 576 patients infected with HCV and treated with a combination of DAAs and a control group of 230 infected patients, of whom 23 were untreated and 213 were treated with an IFN-based regimen. The results found that 10 patients experienced reactivation of the herpes virus (HV), 2 of them with ocular presentation, and 1 of whom progressed to keratouveitis[90]. As no patient in the control group experienced HV reactivation, it appears that treatment with DAAs may lead to transient changes in immunity favoring viral reactivation in some patients, thus demonstrating the need for further studies to clarify the reactivation mechanisms and monitor the HV in these patients, particularly those who have undergone liver transplantation or are of advanced age. Vaccination against the varicella-zoster virus can be performed in non-transplanted patients after treatment[91].

Although its mechanism remains unclear, the combination of ledipasvir/sofosbuvir was related to the development of painless, unilateral, acute visual loss, with visual field deficits and optic disc edema, in a young patient without risk factors who was diagnosed with nonarteritic anterior ischemic optic neuropathy (NAION)[92]. Given the potential of DAAs to decrease the viral load, this treatment was able to reverse NAION induced by hepatitis C in the patient[93].

In the era of IFN-free regimens, the ocular consequences of DAA-based treatments are not clear. However, an increased use of this treatment regimen has generated further studies on the main risks to the visual and other systems. Therefore, medical ophthalmologists and other health professionals should be aware of the ocular effects of these new drugs.

HCV detection sites in the eye and risk of contamination

Kobayakawa detected the virus using polymerase chain reaction (PCR) in the aqueous humor during cataract surgery in some patients[94], and Shimazaki et al. detected the virus in tears and aqueous humor[95]. In a study examining corneoscleral discs from donors seropositive for hepatitis B and C viruses[96], Sengler also detected viral particles in some tissues on PCR, but Laycock et al. did not detect anything in the samples[97]. However, Atas et al. recently identified the virus on PCR in both the aqueous humor and the tears of subjects with anti-HCV-positive antibodies[98].

Another study demonstrated a significant correlation between HCV carriers and the presence of the virus in the cornea, justifying the rejection of potential donors, although no studies have reported cases of HCV transmission via corneal transplantation[99]. Similar studies have emphasized the importance of performing molecular tests to detect HCV nucleic acids (HCV-RNA) in the donor cornea as the best method to detect the transmission potential[100].

The occupational risk of contracting HCV on contact with contaminated blood and fluids is well known. Studies have described cases of contamination through the face and eyes, reinforcing the need of preventive measures against HCV contamination[82].

The presence of the virus in ocular structures, together with the possibility of contamination through the ocular surface, makes HCV an agent of particular risk to the ophthalmologist.

CONCLUSION

Knowledge of the manifestations of the HCV in the eye may aid in the early detection of this serious infection. Many studies have confirmed the association of lacrimal gland dysfunction as a cause of dry eye, and, although less common, of pathological alterations of the posterior pole, especially of the retina, that can occur even during treatment.

Finally, this review reinforces the importance of early suspicion or detection of HCV infection during ophthalmologic examinations, in addition to alerting health professionals, including ophthalmologists, to the risk of contamination during procedures, examinations, and ocular surgeries.

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