10.2478/inmed-2024-0290

TREATMENT REVOLUTION: THE NEW ERA AGAINST HEPATITIS C

Oana Irina Gavril[1,2], Irina Mihaela Eșanu[1,2], Radu Sebastian Gavril[1], Carmen Camelia Buruiană[1], Florin Mitu[1,3,4]
[1]University of Medicine and Pharmacy "Grigore T. Popa" Iasi (Romania)
[2]Clinical Hospital C.F Iasi
[3]Academy of Medical Sciences of Romania
[4]Academy of Romanian Scientists
Corresponding author: Irina Mihaela Eșanu, Radu Sebastian Gavril
E-mail: esanu1925@gmail.com, rgavril87@yahoo.com

Abstract
In recent decades, chronic viral infection C (HCV) has posed a major public health challenge globally, considering the morbidity and mortality associated with this condition, as well as the difficulties related to diagnosis and treatment. Recently, significant advances in medical and pharmaceutical research have led to the development of new direct-acting antiviral therapies (DAAs), marking the beginning of a new era in HCV treatment. These treatments promise cure rates of over 90%, an improved safety profile, and a reduced duration of therapy compared to previous interferon-based regimens. This article aims to examine the evolution of HCV treatment, with a special focus on recent innovations in antiviral therapy. We will analyze the mechanisms of action of DAAs, their efficacy and safety, and their impact on populations with limited access to treatment. Additionally, we discuss the remaining challenges in the path to HCV eradication, including late diagnosis, barriers to treatment access, and the need for long-term monitoring of cured patients. By consolidating data from recent clinical studies and reviewing the specialized literature, this article provides a comprehensive perspective on the current landscape of HCV treatment, highlighting significant progress made and underlining the future directions needed to address remaining challenges. Finally, we reaffirm the importance of an integrated approach, encompassing prevention, early diagnosis, and universal access to innovative treatments, as a cornerstone in the fight against HCV.
Keywords: *chronic viral infection C, new direct acting antiviral therapies, treatment revolution.*

Rezumat
În ultimele decenii, infecția cronică virală C (HCV) a reprezentat o provocare majoră pentru sănătatea publică la nivel global, având în vedere morbiditatea și mortalitatea asociate cu această afecțiune, precum și dificultățile legate de diagnostic și tratament.



Internal Medicine

General Reviews

Recent, progresele semnificative în domeniul cercetării medicale și farmaceutice au dus la dezvoltarea unor noi terapii antivirale cu acțiune directă (DAA), care marchează începutul unei noi ere în tratamentul HCV. Aceste tratamente promit rate de vindecare de peste 90%, un profil de siguranță îmbunătățit și o durată de terapie redusă, comparativ cu regimurile anterioare bazate pe interferon. Articolul de față își propune să examineze evoluția tratamentului pentru HCV, cu un accent special pe inovațiile recente în terapia antivirală.

Vom analiza mecanismele de acțiune ale DAA-urilor, eficacitatea și siguranța acestora, precum și impactul lor asupra populațiilor cu acces limitat la tratament. De asemenea, discutăm provocările rămase în calea eradicării HCV, inclusiv diagnosticarea tardivă, barierile în accesul la tratament și necesitatea monitorizării pe termen lung a pacienților vindecați.

Prin consolidarea datelor din studii clinice recente și revizuirea literaturii de specialitate, acest articol oferă o perspectivă amplă asupra peisajului actual al tratamentului HCV, evidențiind progresele semnificative realizate și subliniind direcțiile viitoare necesare pentru a aborda provocările rămase. În final, reafirmăm importanța unei abordări integrate, care să cuprindă prevenția, diagnosticarea precoce și accesul universal la tratamente inovatoare, ca piatră de temelie în lupta împotriva HCV.

***Cuvinte cheie**: infecție cronică virală C, tratament antiviral oral, revoluția tratamentului*

Introduction

Treatment Regimens

The last 30 years have been a tremendous success regarding translational sciences related to HCV infection[1,2]:

- **1989 -** HCV (non-A non-B hepatitis) was first isolated from serum in 1989 by Choo[3].
- **1990 -** The first screening test for HCV infection appeared in 1990.
- **1991 -** The Food and Drug Administration (FDA) approved, for the first time, treatment for chronic viral hepatitis C in 1991. The treatment consisted of non-pegylated Interferon: alpha 2a or alpha 2b, in monotherapy, involving the administration of 3 million units three times a week. The duration of the treatment was 24 or 48 weeks, depending on the genotype of the C virus. Few patients achieved a sustained virological response (SVR), which signifies undetectable HCV RNA 6 months after the

end of therapy. The cure rate was 6%.

- **1995 -** In 1995, the introduction of Ribavirin in combination with Interferon increased SVR rates to 34-42%[4].
- **2001 -** By the year 2001, alpha interferon was the cornerstone of chronic HCV infection treatment. A major improvement in HCV therapy was the use of pegylated alpha interferon with Ribavirin, resulting in response rates greater than 60%, though dependent on the viral genotype. Pegylated alpha interferon combined with Ribavirin could lead to SVR. The efficiency is proportional to the viral genotype. Thus, HCV genotype 1 and HCV genotype 3 are the most common genotypes worldwide, with HCV genotype 1 being more prevalent in the United States[5]. Treatment with alpha-PegInterferon and Ribavirin results in SVR in 30-50% of patients infected with HCV genotype 1 (29) and 70% of those infected with HCV genotype 3[6]. However, nearly 80% of the subjects undergoing treatment with pegylated interferon and Ribavirin experience side effects of SVR. Many patients were not eligible for antiviral treatment due to intolerance (partly due to Interferon, partly due to Ribavirin), comorbidities, or advanced liver diseases[7]. The most common adverse effect of the dual therapy with pegylated interferon and Ribavirin was the flu-like syndrome (myalgias, headache, loss of appetite, fever, asthenia). Hematological impairments reported for therapy with pegylated interferon and Ribavirin included leukopenia and thrombocytopenia for Interferon and hemolytic anemia for Ribavirin. Other adverse effects in the dual therapy are injection site reactions, alopecia, dermatitis, psychiatric disorders, and exacerbation of pre-existing thyroid dysfunctions. The duration of treatment was determined based on the initial value of HCV RNA, the stage of fibrosis, and the type of viral response to treatment. The standard treatment was 48 weeks.
- **2011 -** Starting 2011, two direct-acting antiviral medications were approved: the N3/N4 protease inhibitors (PIs) Boceprevir and Telaprevir. Hepatitis C virus protease inhibitors (PIs) became the first class of oral antiviral agents used in clinical practice. However, the first generation of PIs had to be combined with pegylated interferon and Ribavirin. The combination of these direct-acting antiviral medications resulted in a sustained virological response (SVR) in 70-80% of cases[8]. Although the efficacy of protease inhibitors for HCV infection increased, new adverse effects emerged. The most common adverse effect in therapy with Boceprevir was reported as dysgeusia, while Telaprevir was noted for anorectal adverse effects. Some already known adverse reactions were exacerbated: anemia in the treatment with Boceprevir and rash in the treatment with Telaprevir.
- **2014 -** Since 2014, several more oral antiviral agents have been approved, allowing for all-oral treatments for HCV, resulting in response rates greater than 90%[10].
  - Sofosbuvir-Ribavirin
  - Ledipasvir/Sofosbuvir-Ribavirin
  - Simeprevir/Sofosbuvir
  - Ombitasvir/Paritaprevir/Dasabuvir-Ribavirin

The interferon-free regimens have few contraindications, minimal side effects, and are administered orally. These therapies are



also effective in hard-to-treat subjects, for example: hepatic cirrhosis, transplant patients, lack of response to previous treatment, or co-infection with the human immunodeficiency viruses (HIV)[11]. As a consequence of this success story, liver transplantation for HCV-related liver disease is already in decline. Survival after liver transplantation for HCV is now similar to other indications for liver transplantation[12,13].

- **2016 -** In 2016, WHO published targets for the global viral cure of HCV infection[14,15]. The positive progress in DAA (Direct-Acting Antivirals) treatment highlighted significant results regarding safety and efficacy - 7 oral antiviral regimens were approved by the FDA for the treatment of chronic viral hepatitis C[16,17]. These antiviral regimens have an SVR (Sustained Virological Response) rate of over 95%.
  - Sofosbuvir/Ledipasvir,
  - Sofosbuvir/Velpatasvir,
  - Ritonavir/Paritaprevir/Ombitasvir/ Dasabuvir,
  - Grazoprevir/Elbasvir,
  - Daclatasvir/Sofosbuvir,
  - Sofosbuvir/Velpatasvir/Voxilaprevir,
  - Glecaprevir/Pibrentasvir DAA therapy targets different points in the replication cycle of the C virus, binding directly to compounds of the replicase complex or initiating the interruption of the RNA chain[18]. The rapid virological responses observed with potent DAA combinations have gradually led to the shortening of treatment duration, with equivalent SVR rates. The guidelines also include 8-week regimens for selected patients, and studies confirm the efficacy of these regimens[19,20].

Conclusion

The evolution of oral antiviral treatment for Hepatitis C represents one of the most significant advancements in the field of infectious diseases and hepatology over the past decades. The transition from interferon-based regimens to the era of Direct-Acting Antivirals (DAAs) has fundamentally altered the approach to treating chronic Hepatitis C Virus (HCV) infection, with profound implications for patient outcomes, public health, and health care systems. The key conclusions from the developments in oral antiviral treatment for Hepatitis C include:

- **Efficacy and safety.** DAAs have demonstrated unparalleled efficacy, with sustained virological response (SVR) rates exceeding 95% across various HCV genotypes and patient populations. This is a significant improvement over previous treatments, which were less effective and often associated with severe

adverse effects. The safety profile of DAAs is also notably better, making treatment possible for a broader range of patients, including those with advanced liver disease and comorbidities.

- **Simplification of treatment.** The advent of DAAs has simplified HCV treatment, reducing the need for complex diagnostic testing to tailor therapy and eliminating the use of interferon. Most DAA regimens are oral, involve once-daily dosing, and offer shorter treatment durations, significantly improving patient adherence and treatment outcomes.
- **Impact of liver disease and transplantation.** Effective DAA therapies have led to a decrease regarding complications associated with chronic HCV infection, such as cirrhosis, liver failure, and hepatocellular carcinoma, potentially reducing the need for liver transplantation. This shift has implications for the management of liver disease and transplantation resources globally.
- **Global health challenge.** Despite the effectiveness of DAAs, challenges remain in the global eradication of HCV. These include diagnosing undiagnosed individuals, ensuring global access to DAAs, and addressing the high costs associated with these medications. Strategies to overcome these challenges are crucial for leveraging the full public health potential of DAAs.
- **Future directions.** Continued research is essential for further improving HCV treatment, including developing vaccines, addressing the small subset of patients who do not achieve SVR with current regimens, and managing HCV resistance. Public health initiatives should also focus on integrating HCV screening and treatment into primary care settings to enhance early detection and treatment access.

The development of oral antiviral treatments for Hepatitis C has been a landmark achievement in modern medicine, offering hope for curing a previously challenging chronic infection. The potential for eliminating HCV as a public health threat is within reach, provided that efforts continue to improve access to these lifesaving treatments, address remaining clinical and public health challenges, and implement effective screening and prevention strategies.

References

1. Mihalache L, Graur LI, Popescu DS, Boiculese L, Badiu C, Graur M. The prevalence of the metabolic syndrome and its components in a rural community. Acta Endocrinologica (Buc). 2012; 8(4): 595-606.

2. Hurjui DM, Niţă O, Graur LI, Mihalache L, Popescu DS, Huţanaşu IC, Ungureanu D, Graur M. Non-alcoholic fatty liver disease is associated with cardiovascular risk factors of metabolic syndrome. Rev Med Chir Soc Med Nat Iasi. 2012 Jul-Sep;116(3):692-9.

3. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989; 244: 359-362.

4. Fried MW, Shiffman ML, Reddy KR et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 2002; 347: 975-982.

5. Messina JP, Humphreys I, Flaxman A et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015; 61: 77-87.

6. Shiffman ML, Suter F, Bacon BR et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. N Engl J Med 2007; 357: 124-134.

7. McHutchison JG, Gordon SC, Schiff ER et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 1998; 339: 1485-1492.

8. Poordad F, McCone J, Bacon BR et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med 2011; 364: 1195-1206.

9. Manns MP, Buti M, Gane E et al. Hepatitis C virus infection. Nar Rec Dis Primers 2017; 3: 17006.

10. Hurjui DM, Niţă O, Graur LI, Mihalache L, Popescu DS, Graur M. The central role of the non alcoholic fatty liver



Internal Medicine

General Reviews

disease in metabolic syndrome. Rev Med Chir Soc Med Nat Iasi. 2012 Apr-Jun;116(2):425-31.

11. Kronfli N, Young J, Wang S et al; Canadian Co-infection Cohort Study Investigators. Liver fibrosis in HIV-hepatitis C virus (HCV) co-infection before and after sustained virologic response: what is the best non-invasive marker for monitoring regression? Clin Infect Dis 2020; 73: 468–477.

12. Terrault NA, Pageaux GP. A changing landscape of liver transplantation: King HCV is dethroned, ALD and NAFLD take over! J Hepatol 2018; 69: 767-768.

13. Gavril OI, Arhire LI, Gavrilescu O, Dranga M, Barboi O, Gavril RS, Popescu R, Cijevschi Prelipcean C, Trifan AV, Mihai C. Role of PNPLA3 in the Assessment and Monitoring of Hepatic Steatosis and Fibrosis in Patients with Chronic Hepatitis C Infection Who Achieved a Sustained Virologic Response. Medicina (Kaunas). 2021 Oct 24;57(11):1153.

14. Gavril OI, Arhire LI, Gavril RS, Zota MI, Gherasim A, Nita O, Drugescu A, Oprescu AC, Esanu IM, Mitu F, Graur M, Mihalache L. Correlations between PNPLA3 Gene Polymorphisms and NAFLD in Type 2 Diabetic Patients. Medicina (Kaunas). 2021 Nov 15;57(11):1249

15. Razavi H, Robbins S, Zeuzem S et al. Hepatitis C virus prevalence and level of intervention required to achieve the WHO targets for elimination in the European Union by 2030: a modelling study. Lancet Gastroenterol Hepatol 2017; 2: 325–336.

16. Singer AW, Reddy KR, Telep LE et al. Direct-acting antiviral treatment for hepatitis C virus infection and risk of incident liver cancer: a retrospective cohort study. Aliment Pharmacol Ther 2018; 47: 1278–1287.

17. Singh S, Facciorusso A, Loomba R et al. Magnitude and Kinetics of Decrease in Liver Stiffness After Antiviral Therapy in Patients With Chronic Hepatitis C: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2018; 16: 27–38.

18. Tamaki N, Kurosaki M, Higuchi M, et al. Genetic Polymorphisms of IL28B and PNPLA3 Are Predictive for HCV Related Rapid Fibrosis Progression and Identify Patients Who Require Urgent Antiviral Treatment with New Regimens. PLoS One 2015; 10: e0137351.

19. Tsui JI, Williams EC, Green PK, Berry K, Su F, Ioannou GN. Alcohol use and hepatitis C virus treatment outcomes among patients receiving direct antiviral agents. Drug Alcohol Depend. 2016; 1(169): 101-109.

20. Zoulim F, Liang TJ, Gerbes AL et al. Hepatitis C virus treatment in the real world: optimising treatment and access to therapies. Gut 2015; 64(11): 1824–1833.