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HEPATITIS C: THE CURRENT STATE OF THE PROBLEM

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Abstract
The article provides a generalized overview of modern virological, diagnostic, and therapeutic aspects of hepatitis C and discusses the latest achievements in this field. Standard therapy for chronic hepatitis C with pegylated forms of interferon-α and ribavirin leads to viral elimination in 40-50% of patients infected with HCV genotype 1 and in 80% of patients infected with HCV genotypes 2 and 3. Today, based on a better understanding of the molecular virology and pathogenesis of hepatitis C, new antiviral therapy strategies are being developed, which are likely to complement existing treatment options in the near future.

Keywords: Hepatitis C, pegylated interferon-α, ribavirin, liver transplantation, sporadic hepatitis C.

Introduction

Infection with the hepatitis C virus (HCV) is one of the most common causes of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC). Decompensated liver cirrhosis, resulting from chronic hepatitis C, is the primary indication for liver transplantation in most industrially developed countries.

Although blood and blood product screening for HCV antibodies (anti-HCV) was introduced in 1991-1992, significantly reducing the incidence of new infections, the number of patients with late-stage complications of chronic hepatitis C is expected to increase over the next 20-30 years—unless new, effective, and widely accessible treatment methods are developed.

Virology

HCV was identified in 1989 as the most common causative agent of post-transfusion and sporadic non-A, non-B hepatitis. It is currently classified under the genus *Hepacivirus*, which, along with human-pathogenic flaviviruses and animal-pathogenic pestiviruses and GB viruses, belongs to the *Flaviviridae* family. Various isolated strains... (the sentence seems to be incomplete; you may provide the rest for a full translation).HCV is classified into six genotypes and multiple subtypes based on sequence homology.HCV is a single-stranded, positive-sense RNA virus with a genome length of approximately 9,600 nucleotides. The HCV genome consists of a 5' untranslated region (5'-NCR), a long open reading frame encoding a polyprotein precursor of approximately 3,000 amino acids, and a 3' untranslated region (3'-NCR).The 5'-NCR contains an *internal ribosomal entry site* (IRES), which enables cap-independent translation of viral RNA in the cytoplasm of the

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host cell. The polyprotein precursor undergoes co- and post-translational processing by cellular and viral proteases, resulting in the formation of distinct structural and non-structural proteins. Structural proteins, including the capsid (C) and envelope proteins (E1 and E2), are located in the N-terminal region of the polyprotein, whereas non-structural proteins (from NS2 to NS5B) are found in the C-terminal region. The cleavage of structural proteins from the polyprotein precursor is mediated by signal peptidase in the endoplasmic reticulum.The amino-terminal third of NS2 and NS3 form an autoprotease that facilitates cleavage between NS2 and NS3. NS3 also contains additional... *(the sentence appears to be incomplete; you may provide the rest for a full translation).*The amino-terminal third of NS3 contains a serine protease responsible for processing subsequent non-structural proteins, while the carboxy-terminal region contains an RNA helicase. The NS4A polypeptide acts as a cofactor for the NS3 serine protease. NS4B induces specific membrane modifications, known as the "membranous web," which serves as a scaffold for the viral replication complex. The function of the NS5A polypeptide remains unclear. NS5B contains RNA-dependent RNA polymerase.Similar to HIV infection, chronic hepatitis C results in the production of up to $\mathbf{10^{12}}$ viral particles per day. This high replication rate, combined with the absence of a "proofreading" function in viral RNA polymerase, leads to the genetic variability of HCV.

Epidemiology

In Western Europe and the United States, approximately 1-2% of the total population (around 170 million people worldwide) has a chronic HCV infection. The virus is transmitted primarily through parenteral routes. Before the introduction of HCV screening, the most common mode of transmission was through blood and blood products.Currently, HCV is mainly transmitted through intravenous drug use, with less frequent transmission occurring through sexual contact, from mother to child, accidental needle sticks, iatrogenic procedures, and other routes. In many cases, the exact mode of transmission cannot be determined, leading to classifications of sporadic hepatitis C.

Clinical Presentation and Natural Course

Acute hepatitis C is usually asymptomatic and progresses to a chronic form in approximately 50-80% of cases. Chronic hepatitis C is typically characterized by a mild, slowly progressive course over many years. Within 20 years, 4-20% of patients develop liver cirrhosis, significantly increasing the risk of hepatocellular carcinoma (HCC). In recent years, various Western countries have reported a rise in HCC incidence and mortality, primarily attributed to the spread of chronic hepatitis C. The natural course of chronic hepatitis C has been studied in several retrospective and prospective studies. Depending on the study population, disease progression has been found to be noticeably more favorable in some studies compared to others.

Factors contributing to a higher frequency and faster progression of liver cirrhosis include:

- Older age at the time of infection
- Male sex
- Alcohol consumption

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Coinfection with hepatitis B virus (HBV), human immunodeficiency virus (HIV), schistosomiasis, as well as iron overload and non-alcoholic fatty liver disease (NAFLD) contribute to a higher frequency and faster progression of liver cirrhosis. Various extrahepatic manifestations can be observed in chronic hepatitis C, primarily mixed cryoglobulinemia, membranoproliferative glomerulonephritis, late-onset cutaneous porphyria, lichen planus, and non-Hodgkin's lymphoma.

Diagnosis

To detect antibodies to hepatitis C, highly sensitive and specific enzyme immunoassays (EIA) of the third generation are available. The detection of HCV RNA through reverse transcription polymerase chain reaction (RT-PCR) is largely standardized and widely accessible. Therefore, the recombinant immunoblot assay (RIBA) as a diagnostic confirmation method is recommended only in special cases, such as in positive EIA results in non-clinical settings or for anti-HCV-positive individuals with negative PCR results for RNA (in cases of false-positive EIA results or after a resolved hepatitis C infection).For determining treatment strategies and monitoring effectiveness, important factors include HCV genotype analysis and the quantitative assessment of viremia. Currently, RT-PCR, branched DNA assay (bDNA), or transcription-mediated amplification (TMA) methods are used for the quantitative determination of HCV RNA. Before starting treatment, liver biopsy is strongly recommended. On one hand, there may not be a clear correlation between histological activity, the stages of cirrhosis or fibrosis, and clinical-laboratory data; on the other hand, this method helps to identify additional etiological factors (such as alcohol use, iron overload, or NAFLD).

Modern Treatment Principles

The modern strategy for treating chronic hepatitis C involves the combined use of pegylated interferon-α (PEG-IFN-α), which is administered subcutaneously once a week, and ribavirin, an orally administered guanosine analogue. Both drugs exert their effects through direct (antiviral) and indirect (immunomodulatory) mechanisms, which have only been partially studied so far.

Indications for Treatment

Treatment is indicated for patients with chronic hepatitis C (i.e., those with elevated transaminase levels for more than 6 months, as well as the presence of anti-HCV antibodies and HCV RNA in the serum), who have, at a minimum, moderate inflammation activity and signs of fibrosis on liver biopsy (i.e., an increased risk of liver cirrhosis). In other cases, indications for treatment are less clearly defined and should be evaluated on an individual basis. Factors considered include the patient's biological age and overall health, the duration of HCV infection, the risk of developing liver cirrhosis, the likelihood of response to treatment, and comorbidities. Given that current treatment methods are quite burdensome for patients, it is essential to take into account the potential negative impact on quality of life when deciding on treatment.

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Prognostic Factors

Factors suggesting a good response to IFN-α therapy include:

- Genotypes 2 or 3 of the virus
- Low viremia levels
- Minimal fibrosis

The virus genotype and the initial concentration of HCV RNA are critical in determining the duration of treatment.

Contraindications

Contraindications for the use of IFN-α and PEG-IFN-α include:

- Decompensated liver cirrhosis (Child-Pugh class C)
- Autoimmune hepatitis or other autoimmune diseases
- Endogenous or exogenous immunosuppressive conditions
- Diagnosed depression or other severe psychiatric disorders
- Epilepsy
- Thrombocytopenia (<50,000/μL) or leukopenia (<2,000/μL)
- Pregnancy

Considering the potential teratogenicity of ribavirin during its use and for 6 months after treatment, both men and women must use reliable contraception methods. Since ribavirin may dose-dependently lead to the development of hemolytic anemia, it is contraindicated in conditions where anemia is poorly tolerated (e.g., lung and heart diseases). In renal failure, ribavirin accumulates in the body.

Side effects

Side effects of IFN-α and PEG-IFN-α include:

- Flu-like symptoms (their severity usually significantly decreases within 1-4 weeks after starting treatment)
- Leukopenia and thrombocytopenia (their occurrence may justify dose reduction)
- Reversible hair loss
- Depression (if left unrecognized, it may lead to suicidal attempts)
- Hyper- or hypothyroidism
- Seizures
- Increased nervous excitability and sleep disturbances

Monitoring

Before starting treatment, in addition to the usual clinical and biochemical blood test parameters, the following should be investigated:

- Thyroid-stimulating hormone levels (to exclude hypo- or hyperthyroidism)
- Antinuclear antibodies and smooth muscle antibodies (to exclude autoimmune hepatitis)
- Antimitochondrial antibodies (to exclude primary biliary cirrhosis)
- Ferritin levels and transferrin saturation percentage (to exclude hemochromatosis)
- Ceruloplasmin levels (to exclude Wilson's disease)

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- HBsAg (to exclude HBV coinfection)
- HIV test

During therapy, regular clinical blood tests, transaminase levels, and kidney function tests should be conducted (every 2 weeks for the first 2 months, then monthly until the end of treatment). During clinical examination, special attention should be paid to psychological changes, particularly possible signs of developing depression. In unclear cases, it is recommended to speak with the patient's relatives. If necessary, after consulting with a psychiatrist, antidepressants may be prescribed for depression developing during IFN-α therapy.

Standard therapy for chronic hepatitis C includes the use of PEG-IFN-α (subcutaneously once a week) in combination with oral ribavirin. If the infection is caused by the 2nd or 3rd HCV genotypes, treatment lasts for 24 weeks, with a daily dose of ribavirin being 800 mg. In the more common 1st HCV genotype, treatment should last for 48 weeks, and the daily dose of ribavirin should range from 1000 mg (for body weight less than 75 kg) to 1200 mg (for body weight more than 75 kg). Indicators of treatment response include normalization of transaminase levels (biochemical response), disappearance of HCV RNA from the blood serum (virological response), reduction of inflammation activity and regression of fibrosis based on histological examination (histological response) at the end of treatment ("end of treatment response" - ETR) or after 6 months of follow-up ("sustained response" - SR). The goal of treatment is sustained viral elimination ("sustained virological response" - SVR). In patients with normal transaminase levels and no detectable HCV RNA 6 months after completing therapy, sustained viral elimination is generally achieved. Patients who did not show HCV RNA in the blood at the end of treatment but had a recurrence of HCV RNA during the 6-month follow-up period are classified as having a relapse of the infection ("relapser"). Patients who have no HCV RNA detected at all during or after treatment are termed as achieving a sustained virological response.

Patients who have not shown any response to treatment are characterized as "nonresponders." For patients who do not experience a decrease in viremia by at least 2 log units after 12 weeks of PEG-IFN-α therapy in combination with ribavirin ("early virological response" - EVR), there is a very low likelihood of achieving sustained virological response (SVR). Therefore, in such cases, treatment may be stopped after 12 weeks. When combining PEG-IFN-α and ribavirin, sustained virological response is achieved in approximately 40-50% of patients with the 1st HCV genotype and around 80% of patients infected with the 2nd and 3rd virus genotypes. If patients are willing to adhere to all recommendations, i.e., have high compliance, the percentage of good treatment response in patients with the 1st virus genotype may be even higher. Unfortunately, in everyday clinical practice, a significant portion of patients do not follow the principles of standard therapy due to contraindications or insufficient compliance. Results from certain studies have shown that even in the absence of a sustained biochemical or virological response to IFN-α therapy, the risk of developing HCC (hepatocellular carcinoma) appears to be reduced in these patients. However, the practical significance of the potential antifibrotic and antiproliferative effects of IFN-α cannot yet be fully assessed, and given the lack of prospective and controlled studies at present, we cannot recommend prolonged interferon therapy for this purpose.For patients who do not respond to therapy with PEG-IFN-α and ribavirin, there are currently no established alternative treatment

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methods. It is only recommended to refer these patients to hepatology centers. Treatment regimens alternative to the use of IFN-α are currently the subject of intensive scientific research. Internationally approved modern regimens for combined use of interferon and ribavirin are being evaluated in many clinical studies. Additionally, various modifications of IFN-α dosage and treatment duration are being explored. Research on combined use of IFN-2 and amantadine, as well as IFN-α, ribavirin, and amantadine ("triple therapy"), is still ongoing and does not yet allow for any recommendations for clinical practice.Currently, a range of alternative treatment methods (either as monotherapy or in combination with IFN-α) are being studied, including the use of histamine, thymosin α-1, ursodeoxycholic acid, and glycyrrhizin.as well as various phytotherapeutic agents, including silymarin.

In general, about 50% of patients with chronic hepatitis C can be completely cured today. Efforts are focused on improving the tolerance of therapy through individualized dosing and treatment duration, as well as optimal monitoring. Approximately 50% of patients do not achieve a sustained positive response to IFN-α-based therapy. For such patients, the development of new strategic treatment approaches is required.

Acute Hepatitis C. Treatment outcomes for acute hepatitis C have been studied in numerous studies with small sample sizes and in one prospective (but uncontrolled) clinical trial involving 44 patients. In the latter study, IFN-α was administered at a dose of 5 million IU daily for 4 weeks, followed by three times a week for the subsequent 20 weeks. A sustained virological response was achieved in 98% of patients. Considering that the rate of spontaneous virus clearance in patients with clinically manifest acute hepatitis C reaches 50%, and that a slight delay in starting therapy still allows for a good response, recent studies recommend adopting a cautious approach to the treatment of patients with clinically manifest acute viral hepatitis C. Patients with acute hepatitis C should be referred to hepatology centers.

Special Groups of Patients. Issues related to the treatment of HCV-infected patients with persistently normal levels of transaminases, children, elderly patients, those with co-infections of HIV or HBV, as well as those who have undergone liver transplantation, should be addressed at hepatology centers.

Additional Measures. It is particularly important to prevent other diseases or liver damage. Along with the exclusion of hepatotoxic substances (especially alcohol and drugs), active vaccination against HAV and HBV in individuals at increased risk is possible (or even indicated).

Monitoring for Possible Development of HCC

In patients with liver cirrhosis, to detect hepatocellular carcinoma (HCC) at an early stage, it is necessary to measure the alpha-fetoprotein level and conduct ultrasound of the liver every 6 months.

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Liver Transplantation

For patients with end-stage liver cirrhosis, the issue of liver transplantation should be considered. After the operation, HCV reinfection of the transplant almost always occurs, although the progression of this infection in the early stages is considered relatively favorable. However, it has been shown that approximately 20-30% of patients will develop cirrhosis in the transplanted liver within 5 years. Treating HCV recurrence after liver transplantation presents significant challenges due to pronounced side effects and a relatively low response rate to therapy .A particularly pressing issue is the shortage of donor organs for transplantation. Therefore, liver transplantation from living donors is becoming increasingly common worldwide. The medical and ethical issues that arise for both donors and recipients should be carefully and critically weighed in each specific case of performing this operation.

New Directions in Antiviral Therapy

Progress in understanding the molecular virological aspects of hepatitis C has allowed for the identification of new treatment targets. Currently, specific inhibitors of the virus's serine protease and RNA helicase, as well as RNA polymerase inhibitors, have been developed and partially tested in clinical trials . In addition to these classic pharmacological approaches, gene therapy is being explored with the aim of blocking HCV replication and gene expression. Based on the concept of insufficient (either quantitatively or qualitatively) cellular immune response in the persistence of the virus, various immunotherapeutic methods are being studied to enhance the immune response against the virus. These include, in particular, RNA vaccination and vaccination with peptides or proteins

Vaccine Development

The creation of a recombinant vaccine against HCV is hindered by the significant genetic variability of the virus . Furthermore, the criteria for immune protection in hepatitis C are not yet fully defined. At present, we do not have either passive or active preventive vaccination against HCV infection. Analysis of current data suggests that developing "sterilizing" immunity is challenging. A more realistic approach seems to be the development of immunity that can prevent the development of chronic infection.

Practical Conclusions

HCV infection is one of the most common causes of chronic hepatitis, liver cirrhosis, and HCC. Treatment is indicated for patients with chronic hepatitis C who have at least a moderate degree of inflammation and signs of fibrosis in liver biopsy, in the absence of contraindications. The standard therapy involves the combined use of PEG-IFN-a and ribavirin for 48 weeks (for genotype 1 HCV) or 24 weeks (for genotypes 2 and 3). In this approach, a sustained virological response is achieved in 40-50% of patients with genotype 1 and in 80% of patients with genotypes 2 and 3. Currently, numerous new antiviral treatment directions are being developed, which will likely complement the existing therapeutic options in the near future.

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