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REVIEW ARTICLE

Review Article on Recent Development in Hepatitis C

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ABSTRACT

The biological differences between genotypes make genotyping important for decision-making regarding disease management and therapeutic intervention. HCV infection is estimated to be the commonest liver disease in renal dialysis patients with a prevalence rate of 5% to as high as 50% in some centers. Most natural hepatitis C virus (HCV) infection elicits poor immune responses and 75% to 85% of HCV infections become chronic; therefore, the development of an effective vaccine is of paramount importance. HCV was discovered in 1988. Hepatitis C virus (HCV) is a major cause of chronic hepatitis worldwide, which finally leads to development of hepatocellular carcinoma. Hepatitis C virus (HCV) translation initiation depends on an internal ribosome entry site (IRES). Previously we will study the detail and treatment of HCV. Hepatitis C virus (HCV) causes persistent infection and induces chronic hepatitis, liver cirrhosis and finally hepatocellular carcinoma. Current therapies for HCV infection have not been satisfactory, and more effective anti-viral treatments are needed. Despite progressive advances, therapy with interferon and ribavirin has been the mainstay of treatment for chronic hepatitis C for over a decade. Therefore, the development of further effective therapeutic agents against HCV is an urgent public health requirement. Anti-HCV activity of certain 50-O-masked analogues would arise from a new type of mechanism that does not involve the 50-O-triphosphorylation process. There is still room for the discussion on the 50-O-masking effect because certain carbon–oxygen bonds, for example, the carboxylic ester bond of compound (i.e., the benzoate moiety in compound) are often hydrolyzed in cultured cells.

Keywords: Hepatitis C, Ciluprevira, NS3 protease.

INTRODUCTION:

Hepatitis C virus (HCV) is major health problem affecting 170 million people worldwide. The infection with the HCV is the leading cause of chronic hepatitis worldwide, progressing to liver cirrhosis in approximately 20% of patients; HCV is a positive strand RNA virus of approximately 9.6 Kb in length. [1]. The prevalence of HCV infection is higher in patients on hemodialysis than in general population Patients with kidney diseases are more prone to develop HCV infection secondary to blood transfusions, hemodialysis and even renal transplantation [2]. First, substantial sequence diversity exists among HCV strains isolated within and between geographic areas and there are at least 6 HCV genotypes associated with more than 50 subtypes. Vaccine Development for Hepatitis C lessons from the past turn into promise for the future [3, 4, and 5]. It has been discovered that C virus (HCV) Presents considerable nucleotidevariation and has many genotype [6]. One of the major issues regarding the pathogenesis of HCV-associated liver lesion is whether the HCV proteins have direct effects on pathological phenotypes [7]. HCV-RNA has been detected in saliva and in salivary glands from patients with sialadenitis by polymerase chain reaction. However, morphological evidence of HCV replication in salivary gland cells is needed to support role for HCV in causing sialadenitis or Sjogren's syndrome [8]. Hepatitis C virus (HCV), which is a small, enveloped virus belonging to a new genus within the *Flaviridae* family of viruses [9]. Original magnification, 31,000. Counterstained with safranine [10]. Hepatitis C virus is a number of the *flaviviridae* family, which includes the classical flaviviruses and the animal pestiviruses. The virion contains a positive single-stranded

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RNA genome of 9.5 kilobase which consist of 5 and 3 untranslated regions important for translation of viral proteins and replication of the virus [11].

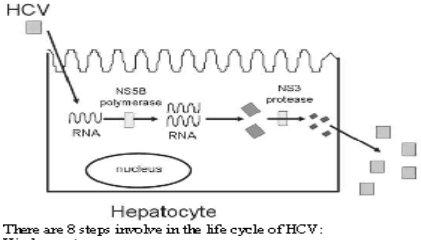
CAUSE OF HEPATITIS C:

Hepatitis C virus (HCV), the major causative agent of non-A, non-B hepatitis [12]. Hepatitis can have numerous causes, such as excessive alcohol consumption or infection by certain bacteria or viruses. One common cause of hepatitis is infection with one of several types of viruses (e.g., hepatitis A, B, or C viruses) [13].

Alcoholism was associated with HCV even in people who did not show classic risk factors, such as intravenous drug abuse or blood transfusions: [14]

Transmission of hepatitis C (HCV): Hepatitis C virus is primarily spread by direct contact with infected blood. Alter MJ et al., (1993). Intranasal cocaine use, non-professional tattooing and piercing have become identified as possible modes of transmission. Abildgaard N et al., (1991). Nosocomial transmission has been reported in dialysing units. Seme K et al., (1995). Occupational needlestick injuries from anti-HCV sources result in seroconversion in 2-8% of recipients Howard RJ et al., (1997). Sexual transmission is possible but rare and correlates with high-risk sexual practices. The frequency of sexual transmission is estimated to approximately 5%, whereas for HIV it is 10-15% and for HBV 30%. Utsumi T et al.,(1995). Mother-to-infant transmission has been observed with the risk below 5%, unless mother is co-infected with HIV. Tor J et al., (1990). Hepatitis C virus transmission by breast feeding is unusual. Household transmission is uncommon. Kudesia B et al., (1995).

Life Cycle of Hepatitis C (HCV): Hepatitis C inhibitors:



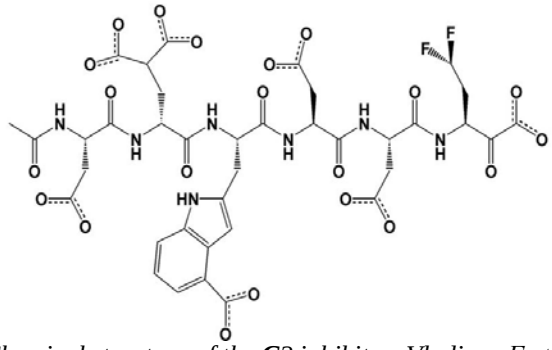
There are 8 steps involve in the life cycle of HCV:
Viral receptor
Complex
Hepatocyte
IFN/cytokinereceptors
(a) Natural killer, cell-receptors
(b) MHC class I molecules
(c) Legend
Life cycle Structures for defense (Viral clearance)
1. Binding of HCV to a cell surface receptor a) occupation of receptor leads to signal
2. Cytoplasmic release and uncoating of the viral RNA genome transduction (anti-viral status)
3. IRES-mediated translation b) binding of NK cells leads to destruction of
4. Polyprotein processing by cellular and viral proteases infected cell
5. RNA replicationc) T cell epitopes of HCV presented on the MHC
6. Packaging and assembly molecules target the infected cells for the
7. Virion maturation attack by HCV-specific cytotoxic T-cells
8. Release from the host cell

NS3 protease inhibitors:

The NS3 protease has been considered as one of the most attractive targets for anti-HCV therapy because it is essential active site serine residue such that the P1 region of the bound inhibitor mimics the transition state of substrate hydrolysis. A novel class of NS3 protease inhibitors has been made based on the C-terminal tetrapeptide cleavage product (P1'–P4') However, the most potent inhibitors reported to date contain either a 4-substituted proline or a 3,4-disubstituted proline as P2 residue. The potency of these inhibitors are further enhanced through a depeptidize process using 2- azabicyclo ,heptane carboxylic acid as a surrogate. Hsin-Yuan Wei et al., (2008).

NS3 serine protease of hepatitis C virus:

The complex NS3/4A has been identified as a promising target for antiviral drugs effective against the HCV. Recently, it has been reported that N-terminal cleavage products of the substrate form competitive inhibitors of the NS3 protease activity. These native inhibitors (typically hexapeptides) served as the basis for designing substrate-based inhibitors, sequences of which were derived from the polyprotein precursor sites cleaved by the NS3 protease.

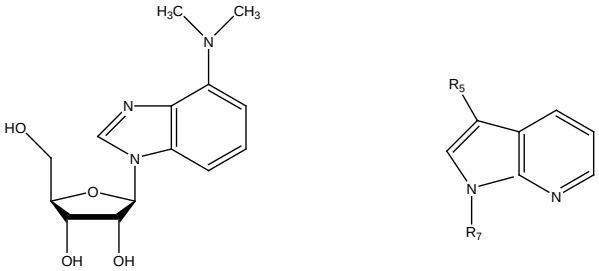


*Chemical structure of the **C**2 inhibitor. Vladimır F et al., (2004).**VX-950, SCH 503034:***

Currently there are two product-derived linear peptidomimetics, VX-950and SCH 503034 reported to be in phase II clinical trials and found linear HCV NS3/4A. protease inhibitors has highlighted that a trisubstituted cyclopentane dicarboxylic acid could be a novel P2 mimic of the frequently used N-acyl-(4R)-hydroxyproline, exemplified by inhibitor. The SAR from HCV NS3 protease inhibitors containing P1 carboxylic acid with either a P3 hydrazine- or P4 NH-Boc-functionalized macrocyclic moiety clearly indicated a preference for 14-membered rings, exemplified by the P2 cyclopentane inhibitors. Marcus Back et al., (2007).

Currently, combinations of pegylated interferons and ribavirin are the leading therapy for hepatitis

C virus. Many classes of nucleoside and non-nucleoside inhibitors of NS5B RdRp have been identified and patent applications in pursuit of a better treatment for HCV.



***1**, EC50: 7.0 μM, CC50 300 μM*
***2**: R5 = H;R 7 = H*
***3**: R5 = H;R 7 = ribofuranosy*
***4**: R5 = CN;R7= ribofuranosyl*
***5**: R5 = CONH2; R7 = ribofuranosy*
Adenosine lead derivative (1) and Toyocamycin (4) analogues. Chamakura VNS Varaprasad et al (2007).

NEW HCV ANTIVIRAL AGENTS

Vincent S et al. (2009).

S.No	Class	Drugs
1.	Protease inhibitors	Ciluprevira, ITMN-191/R-7227 Telaprevirb, Boceprevirb GS-9132/ACH-806[a], BI-1335 TMC-435350, MK-7009
2.	Polymerase inhibitors Nucleoside analogues	Valopicitabinea, R-1626/ R-1479b R-7128/PSI-6130, MK-0608
3.	Nonnucleoside analogues	HCV-796[a], A-837093 XTL-2125[a], ANA-598 GS-9190a,PF-00868554 VHC-759, BI-1941, MK-3281

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