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Short Guide to Hepatitis C

2012

edited by
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2012 Edition

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2012 Flying Publisher ***Short Guide to Hepatitis C***
is freely available from www.FlyingPublisher.com
thanks to an educational grant provided by

Roche

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Design: Attilio Baghino, www.baghino.com
ISBN: 978-3-942687-11-9
Printed in Germany by Druckhaus Süd, www.druckhaus-sued.de

Preface

Hepatitis C is a rapidly developing area of medicine – diagnostic tools are ever more refined, and entirely new treatments and treatment strategies are arriving, with more on the horizon. And because the virus affects such a large and varying population – up to 170 million at last count – we think it is important to have a pocket reference especially devoted to hepatitis C. We look forward to your comments on the usefulness of our **2012 Short Guide to Hepatitis C**, which is an expansion and update of the HCV chapters in **Hepatology – A Clinical Textbook** (2012), also published by Flying Publisher. As always, we invite qualified people everywhere to translate this book into other languages, and make them available widely. This web-based free-of-charge concept is made possible by unrestricted educational grants from the pharmaceutical industry and has allowed the material to reach countries usually not covered by print media. We are convinced that this new pocket guide concept, focusing here on hepatitis C, will become a valuable source of information for our readers.

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The Editors
March 2012

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Abbreviations

ADV: adefovir dipivoxil
AHA: autoimmune haemolytic anaemia
ALT: alanine aminotransferase
AST: aspartate aminotransferase
BID: twice a day
BOC: bocepravir
cccDNA: covalently closed circular DNA
CP: Child-Pugh
EHM: extrahepatic manifestation
ER: endoplasmic reticulum
EVR: early virologic response
GH: growth hormone
GM-CSF: granulocyte macrophage colony-stimulating factor
GN: glomerulonephritis
HBsAg: hepatitis B surface antigen
HBV: hepatitis B virus
HCV: hepatitis C virus
HCV RNA: riboneucleic acid of hepatitis C virus
HCC: hepatocellular carcinoma
IFN alfa: interferon alfa
IGF-1: insulin growth factor-1
INR: international normalised ratio
IPF: idiopathic pulmonary fibrosis
ITP: immune thrombocytopenic purpura
LDL: low density lipoproteins
MELD: Model for End-Stage Liver Disease
NHL: non-Hodgkin lymphoma
NPV: negative predictive value
NTR: non-translated regions
PCR: polymerase chain reaction
PCT: porphyria cutanea tarda
PEG-IFN: pegylated interferon
PT: prothrombin time
QD: once a day
QW: once a week
RF: rheumatoid factor
RVR: rapid virologic response
SSRI: selective serotonin reuptake inhibitor
SVR: sustained virologic response
TGF: transforming growth factor
RBV: ribavirin
TID: three times a day
TLP: telapravir
TSH: thyroid stimulating hormone

Table of Contents

1. Epidemiology, Transmission and Natural History

Christoph Boesecke and Jan-Christian Wasmuth

Epidemiology

Hepatitis C is a disease with a significant global impact. According to the World Health Organization there are 130-170 million people infected with hepatitis C virus (HCV). There are considerable regional differences. In some countries, e.g., Egypt, the prevalence is as high as 22% (WHO 2011). In Africa and the Western Pacific the prevalence is significantly higher than in North America and Europe (RKI 2004). It is estimated that there are 2-5 million HCV-positive persons in Europe. Certain groups are preferentially affected, like injection drug users. In Europe and the United States chronic hepatitis C is the most common chronic liver disease. The majority of liver transplants performed in these regions are for chronic HCV. It is difficult to determine the number of new HCV infections, as most acute cases are not noticed clinically.

Transmission

Parenteral exposure to the hepatitis C virus is the most efficient means of transmission. The majority of patients infected with HCV in Europe and the United States acquired the disease through intravenous drug use or blood transfusion, the latter of which has become rare since routine testing of the blood supply for HCV began. The following possible routes of infection have been identified in blood donors (in descending order of transmission risk):

- Injection drug use
- Blood transfusion
- Sex with an intravenous drug user
- Having been in jail more than three days
- Religious scarification
- Having been struck or cut with a bloody object
- Pierced ears or body parts
- Immunoglobulin injection

Very often in patients with newly diagnosed HCV infection no clear risk factor can be identified.

Factors that may increase the risk of HCV infection include greater numbers of sex partners, history of sexually transmitted diseases, and failure to use a condom. Whether underlying HIV infection increases the risk of heterosexual HCV transmission to an uninfected partner is unclear. The seroprevalence of HCV in MSM (men who have sex with men) ranges from about 4 to 8%, which is higher than the HCV prevalence reported for general European populations, increasing globally over the last decade (Boesecke 2011).

The risk of perinatal transmission of HCV in HCV RNA-positive mothers is estimated to be 5% or less (Ohto 1994). Cesarean section has not been shown to reduce transmission. There is no evidence that breastfeeding is a risk factor.

Hemodialysis risk factors include blood transfusions, the duration of hemodialysis, the prevalence of HCV infection in the

dialysis unit, and the type of dialysis. The risk is higher with in-hospital hemodialysis vs peritoneal dialysis.

Contaminated medical equipment, traditional medicine rites, tattooing, and body piercing are considered rare transmission routes.

There is some risk of HCV transmission for health care workers after unintentional needle-stick injury or exposure to other sharp objects.

Acute Hepatitis

After HCV inoculation, there is a variable incubation period. HCV RNA in blood (or liver) can be detected by PCR within several days to eight weeks (Hoofnagle 1997). Aminotransferases become elevated approximately 6-12 weeks after exposure (range 1-26 weeks) and they tend to be more than 10-30 times the upper limit of normal. HCV antibodies can be found about 8 weeks after exposure although it may take several months. However, the majority of newly infected patients will be asymptomatic and have a clinically non-apparent or mild course. Periodic screening for infection may be warranted in certain groups of patients who are at high risk of infection, e.g., homosexually active patients with HIV infection. Symptoms include malaise, nausea, and right upper quadrant pain. In patients who experience such symptoms, the illness typically lasts for 2-12 weeks. Along with clinical resolution of symptoms, aminotransferases will normalize in about 40% of patients. Loss of HCV RNA, which indicates a hepatitis C cure, occurs in fewer than 20% of patients. Fulminant hepatic failure due to acute HCV infection may happen in patients with underlying chronic hepatitis B virus infection (Chu 1999).

Chronic Hepatitis

The risk of chronic HCV infection is high. About 75% of patients with acute hepatitis C do not eliminate HCV RNA and progress to chronic infection. Most of these will have persistently elevated

liver enzymes in follow-up. Hepatitis C is considered to be chronic after six months. Once chronic infection is established, there is a very low rate of spontaneous clearance.

Most patients with chronic infection are asymptomatic or have only mild nonspecific symptoms as long as cirrhosis is not present (Lauer 2001, Merican 1993). The most frequent complaint is fatigue. Less common manifestations are nausea, weakness, myalgia, arthralgia, and weight loss (Merican 1993).

Aminotransferase levels can vary considerably over the natural history of chronic hepatitis C.

Natural History

The risk of developing cirrhosis within 20 years is estimated to be around 10 to 20%, with some studies showing estimates of up to 50% (Poynard 1997, Wiese 2000, Sangiovanni 2006). About 30% of patients will not develop cirrhosis for at least 50 years (Poynard 1997). It is not completely understood why there are such differences in disease progression. An influence of host and viral factors has to be assumed.

Cirrhosis and Hepatic Decompensation

Complications of hepatitis C occur almost exclusively in patients who have developed cirrhosis. Non-liver-related mortality is higher in cirrhotic patients as well.

The risk for decompensation is estimated to be close to 5% per year in cirrhotics (Poynard 1997). Once decompensation has developed, the 5-year survival rate is roughly 50% (Planas 2004). Liver transplantation is then the only effective therapy. Hepatocellular carcinoma (HCC) also develops solely in patients with cirrhosis (in contrast to chronic hepatitis B).

Disease progression

Chronic HCV progression may differ depending on several factors. Other factors not yet identified may also be important.

Age and gender: More rapid progression is seen in males older than 40-55 (Svirtlih 2007), while a less rapid progression is seen in children (Child 1964).

Ethnic background: A slower progression has been noted in African-Americans (Sterling 2004).
HCV-specific cellular immune response: Genetic determinants like HLA expression (Hraber 2007) probably guide the inflammatory response.
Alcohol intake: Even moderate amounts of alcohol increase HCV replication, enhance the progression of chronic HCV, and accelerate liver injury (Gitto 2009).
Daily use of marijuana: may cause a more rapid progression.
Other host factors: TGF B1 phenotype or PNPLA-3 (adiponutrin) and fibrosis stage are correlated with fibrosis progression rate (Zimmer 2011). Moderate to severe steatosis correlates with developing hepatic fibrosis.
Viral coinfections: HCV progression is more rapid in HIV-infected patients. Acute hepatitis B in a patient with chronic hepatitis C may be more severe. Liver damage is usually worse and progression faster in patients with dual HBV/HCV infections.
Geography and environmental factors: Clear, but not understood (Lim 2008).
Use of steroids: increases HCV viral load.
Viral factors: There seems to be no significant role of different genotypes and quasispecies on fibrosis progression or outcome. However, coinfection with several genotypes may have a worse outcome as compared to monoinfection. Liver biopsy is the best predictor of disease progression (Gebo 2002).

In patients with cirrhosis, the MELD score (Model for End-Stage Liver Disease) and the Child score (Table 1.1) are used to stage disease and to describe the prognosis. An online calculator and further information can be found at the website of The United Network for Organ Sharing (UNOS) (http://www.unos.org).

For details on extrahepatic manifestations, please see Chapter 7.

Table 1.1 – Child-Pugh classification of severity of liver disease (Child 1964).

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin, mg/dL	<2	2-3	>3
Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time			
Prothrombin time	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3
Encephalopathy	None	Grades 1-2	Grades 3-4

A total score of 5-6 is considered stage A (well-compensated disease); 7-9 is stage B (significant functional compromise); and 10-15 is stage C (decompensated disease). These grades correlate with one- and two-year patient survival: stage A - 100 and 85 percent; stage B - 80 and 60 percent; and stage C - 45 and 35 percent.

2. HCV Structure and Viral Replication

Bernd Kupfer

Taxonomy and Genotypes

The hepatitis C virus (HCV) is in the Hepacivirus genus of the *Flaviviridae* family. To date, six major HCV genotypes with a large number of subtypes within each genotype are known (Simmonds 2005). The high replication rate of the virus together with the error-prone RNA polymerase of HCV is responsible for the large interpatient genetic diversity of HCV strains. Moreover, the extent of viral diversification of HCV strains within a single HCV-positive individual increases significantly over time resulting in the development of quasispecies (Bukh 1995).

Viral Structure

Structural analyses of HCV virions are very limited because for a long time the virus was difficult to cultivate in cell culture systems, a prerequisite for yielding sufficient virions for electron microscopy. Moreover, serum-derived virus particles are associated with serum low-density lipoproteins (Thomssen 1992), which makes it difficult to isolate virions from serum/plasma of subjects via centrifugation.

It has been shown that HCV virions isolated from cell culture have a spherical envelope containing tetramers (or dimer of heterodimers) of the HCV E1 and E2 glycoproteins (Heller 2005, Wakita 2005, Yu 2007). Inside the virions a spherical structure has been observed (Wakita 2005) representing the nucleocapsid (core) that harbours the viral genome.

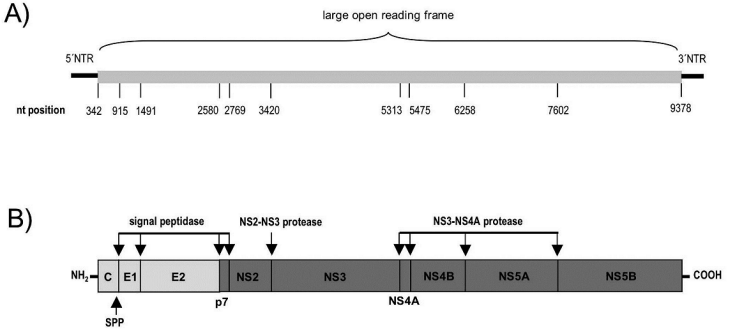

Figure 2.1 – Genome organization and polyprotein processing.
A) Nucleotide positions correspond to the HCV strain H77 genotype 1a, accession number NC_004102. nt, nucleotide; NTR, nontranslated region. B) Cleavage sites within the HCV precursor polyprotein for the cellular signal peptidase, the signal peptide peptidase (SPP) and the viral proteases NS2-NS3 and NS3-NS4A, respectively.

Genome Organization

The genome of the hepatitis C virus consists of one 9.6 kb single-stranded RNA molecule with positive polarity. Similar to other positive-strand RNA viruses, the genomic RNA of hepatitis C virus serves as messenger RNA (mRNA) for the translation of viral proteins. The linear molecule contains a single open reading frame (ORF) coding for a precursor polyprotein of approximately 3000 amino acid residues flanked by two regulatory nontranslated regions (NTR) (Figure 2.1).

Table 2.1 – Size and main function of HCV proteins. MW, molecular weight in kd (kilodalton).

Protein	MW	Function
Core	21 kd	Capsid-forming protein. Regulatory functions in translation, RNA replication, and particle assembly.
F-protein or ARFP	16-17 kd	Unknown.
Envelope glycoprotein 1 (E1)	35 kd	Transmembrane glycoprotein in the viral envelope. Adsorption, receptor-mediated endocytosis.
Envelope glycoprotein 2 (E2)	70 kd	Transmembrane glycoprotein in the viral envelope. Adsorption, receptor-mediated endocytosis.
p7	7 kd	Forms an ion-channel in the endoplasmic reticulum. Essential formation of infectious virions.
NS2	21 kd	Portion of the NS2-3 protease which catalyses cleavage of the polyprotein precursor between NS2 and NS3 (Figure 2.1).
NS3	70 kd	NS2-NS3 protease, cleavage of the downstream HCV proteins (Figure 2.1). ATPase/helicase activity, binding and unwinding of viral RNA.
NS4A	4 kd	Cofactor of the NS3-NS4A protease.
NS4B	27 kd	Crucial in HCV replication. Induces membranous web at the ER during HCV RNA replication.
NS5A	56 kd	Multi-functional phosphoprotein. Contains the IFN α sensitivity-determining region (ISDR) that plays a significant role in the response to IFN α-based therapy.
NS5B	66 kd	Viral RNA-dependent RNA polymerase. NS5B is an error-prone enzyme that incorporates wrong ribonucleotides at a rate of approximately 10^{-3} per nucleotide per generation.

HCV Proteins

Translation of the HCV polyprotein is initiated through involvement of some domains in the NTRs of the genomic HCV RNA. The resulting polyprotein consists of ten proteins that are co-translationally or post-translationally cleaved from the polyprotein. In addition, the F (frameshift) or ARF (alternate reading frame) protein has been explored (Walewski 2001). During translation ARFP is the product of ribosomal frameshifting within the core protein-encoding region.

Viral Lifecycle

The recent development of small animal models and more efficient *in vitro* HCV replication systems has offered the opportunity to analyse in detail the different steps of viral replication (Figure 2.2).

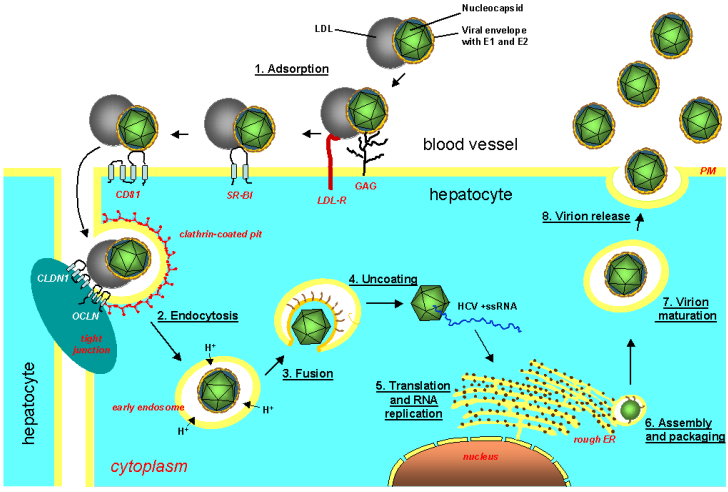

Figure 2.2 – Model of the HCV lifecycle. Designations of cellular components are in italics. For a detailed illustration of viral translation and RNA replication, see Pawlotsky 2007. HCV +ssRNA, single stranded genomic HCV RNA with positive polarity; rough ER, rough endoplasmic reticulum; PM, plasma membrane. For other abbreviations see text.

Adsorption and viral entry

A cascade of virus-cell interactions is necessary for the infection of hepatocytes. The precise mechanism of viral entry is complex and still not completely understood. The current model of viral adsorption assumes that HCV is associated with low-density lipoproteins (LDL). The binding step includes binding of the LDL component to the LDL-receptor (LDL-R) on the cell surface (Agnello 1999) and simultaneous interaction of the viral

glycoproteins with cellular glycosaminoglycans (GAG) (Germi 2002). This initiation step is followed by consecutive interactions of HCV with scavenger receptor B type I (SR-BI) (Scarselli 2002) and the tetraspanin CD81 (Pileri 1998). More recent findings indicate subsequent transfer of the virus to the tight junctions, a protein complex located between adjacent hepatocytes. Two components of tight junctions, Claudin-1 (CLDN1) and occludin (OCLN) have been shown to interact with HCV (Evans 2007, Ploss 2009). Although the precise mechanism of HCV uptake in hepatocytes is still not clarified, these cellular components may represent the complete set of host cell factors necessary for cell-free HCV entry. Interaction of HCV with CLDN1 and OCLN seems to induce the internalisation of the virion via clathrin-mediated endocytosis (Hsu 2003). Subsequent HCV E1-E2 glycoprotein mediation fuses the viral envelope with the endosome membrane (Meertens 2006).

Despite having identified several host factors that probably interact with the viral glycoproteins, the precise mechanisms of interaction still need to be investigated.

Translation and posttranslational processes

As a result of the fusion of the viral envelope and the endosomic membrane, the genomic HCV RNA is released into the cytoplasm of the cell (uncoating). The viral genomic RNA possesses a nontranslated region (NTR) at each terminus. It contains an internal ribosome entry site (IRES) involved in ribosome binding and subsequent initiation of translation (Tsukiyama-Kohara 1992). The synthesized HCV precursor polyprotein is subsequently processed by at least four distinct peptidases. The cellular signal peptidase (SP) cleaves the N-terminal viral protein's immature core protein, E1, E2, and p7 (Hijikata 1991), while the cellular signal peptide peptidase (SPP) is responsible for the cleavage of the E1 signal sequence from the C-terminus of the immature core protein, resulting in the mature form of the core (McLauchlan 2002). The E1 and E2 proteins remain within the lumen of the ER where they are subsequently N-glycosylated

with E1 having 5 and E2 harbouring 11 putative N-glycosylation sites (Duvet 2002). The remaining HCV proteins are posttranslationally cleaved by the viral NS2-NS3 and the NS3-NS4A protease, respectively.

HCV RNA replication

The process of HCV RNA replication is poorly understood. The key enzyme for viral RNA replication is NS5B, an RNA-dependent RNA polymerase (RdRp) of HCV. After the RdRp has bound to its template, the NS3 helicase is assumed to unwind putative secondary structures of the template RNA in order to facilitate the synthesis of minus-strand RNA (Jin 1995, Kim 1995). In turn, the newly synthesized antisense RNA molecule serves as the template for the synthesis of numerous plus-stranded RNA. The resulting sense RNA may be used subsequently as genomic RNA for HCV progeny as well as for polyprotein translation. Another important viral factor for the formation of the replication complex appears to be NS4B, which is able to induce an ER-derived membranous web containing most of the non-structural HCV proteins including NS5B (Egger 2002).

Assembly and release

After the viral proteins, glycoproteins, and the genomic HCV RNA have been synthesized these components have to be arranged in order to produce infectious virions. Viral assembly is a multi-step procedure involving most viral components along with many cellular factors. Recent findings suggest that viral assembly takes place within the endoplasmic reticulum (Gastaminza 2008) and that lipid droplets are involved in particle formation (Miyanari 2007, Shavinskaya 2007). However, the precise mechanisms for the formation and release of infectious HCV particles are still unknown.

Model systems for research

Small animal models. Recently, substantial progress was made in establishing two mouse models for HCV infection via genetically humanized mice (Dorner 2011). These models will be

useful to investigate the early steps of HCV infection *in vivo*. Moreover, the approach should be suitable for the evaluation of HCV entry inhibitors and vaccine candidates.

A second group of investigators depleted murine hepatocytes and cotransplanted human CD34(+) hematopoietic stem cells and hepatocyte progenitors into transgenic mice leading to efficient engraftment of human leukocytes and hepatocytes, respectively (Washburn 2011). As a consequence, HCV infection induced liver inflammation, hepatitis, and fibrosis. Furthermore, due to the cotransplantation of CD34(+) human hematopoietic stem cells, an HCV-specific T cell immune response was detected.

Both strategies are promising and have already delivered new insights into viral replication and the pathogenesis of HCV but need to be improved in order to acheive higher HCV replication rates as well as to better study the HCV-specific antibody response.

3. Diagnostic Tests in Acute and Chronic Hepatitis C

Christian Lange and Christoph Sarrazin

Hepatitis C is often diagnosed accidentally and, unfortunately, remains heavily underdiagnosed. HCV diagnostics should be performed thoroughly in all patients presenting with increased aminotransferase levels, with chronic liver disease of unclear etiology and with a history of enhanced risk of HCV transmission.

Serologic Assays

With 2nd generation enzyme-linked immunoassays (EIAs), HCV-specific antibodies can be detected approximately 10 weeks after infection (Pawlotsky 2003b). To narrow the diagnostic window from viral transmission to positive serological results, a 3rd generation EIA has been introduced that includes an antigen from the NS5 region and/or the substitution of a highly immunogenic NS3 epitope, allowing the detection of anti-HCV antibodies approximately four to six weeks after infection with a sensitivity of more than 99% (Colin 2001). Anti-HCV IgM measurement can narrow the diagnostic window in only a minority of patients and cannot discriminate between acute and chronic hepatitis C.

False-positive results are more frequent in patients with rheuma factors and in populations with a low hepatitis C prevalence, for example in blood and organ donors. False-negative HCV antibody testing may occur in patients on hemodialysis or in severely immunosuppressed patients or in hematological malignancies.

One **quantitative HCV core antigen assay** (Architect HCV Ag, Abbott Diagnostics) has been approved so far. This assay comprises 5 different antibodies, is highly specific (99.8%) and shows somewhat less sensitivity for determination of chronic hepatitis C as HCV RNA measurement (Morota 2009). False-negative results are obtained in patients with impaired immunity (Mederacke 2009, Medici 2011). For careful monitoring of treatment with standard dual combination therapies or directly acting antiviral agents, prospective studies have to be performed to determine proper rules and time points for response-guided treatment algorithms.

Nucleic Acid Testing for HCV

Because of the importance of an exact HCV RNA load determination for therapeutic management, the World Health Organization (WHO) established the HCV RNA international standard based on international units (IU) which is used in all clinically applied HCV RNA tests. Currently, several HCV RNA assays are commercially available.

Qualitative HCV RNA tests include the **qualitative RT-PCR**, of which the Amplicor™ HCV 2.0 (Roche, USA) is an FDA- and CE-approved RT-PCR system for qualitative HCV RNA testing that allows detection of HCV RNA concentrations down to 50 IU/ml of all HCV genotypes (Nolte 2001).

Transcription-mediated amplification- **(TMA)-based qualitative HCV RNA detection** has a very high sensitivity (lower limit of detection 5-10 IU/ml) (Sarrazin 2002, Hendricks 2003). A commercially available TMA assay is the Versant™ HCV RNA Qualitative Assay (Siemens, Germany). This system is

accredited by FDA and CE and provides an extremely high sensitivity, superior to RT-PCR-based qualitative HCV RNA detection assays (Sarrazin 2000, Sarrazin 2001, Hofmann 2005).

HCV RNA quantification can be achieved either by **target amplification techniques** (competitive and real-time PCR) or by **signal amplification techniques** (branched DNA (bDNA) assay). Several FDA- and CE-approved standardised systems are commercially available. The Cobas Amplicor™ HCV Monitor is based on a competitive PCR technique whereas the Versant™ HCV RNA Assay is based on a bDNA technique. Both have restricted lower limits of detection (500-615 IU/ml). More recently, the Cobas TaqMan assay and the Abbott RealTime™ HCV test, both based on real-time PCR technology, have been introduced and now replace the qualitative and quantitative methods.

All commercially available HCV RNA assays are calibrated to the WHO standard based on HCV genotype 1. It has been shown that results may vary significantly between assays with different HCV genotypes despite standardisation (Chevaliez 2007, Vehrmeren 2008). The **Cobas TaqMan** assay makes both highly sensitive qualitative (limit of detection approx. 10 IU/ml) and linear quantitative HCV RNA detection (35-107 IU/ml) feasible with high specificity and excellent performance in one system with complete automation. The **Abbott RealTime**™ HCV Test provides a lower limit of detection of 12 IU/ml, a specificity of more than 99.5% and a linear amplification range from 12 to 10,000,000 IU/ml independent of the HCV genotype (Michelin 2007, Sabato 2007, Schutten 2007, Vermehren 2008).

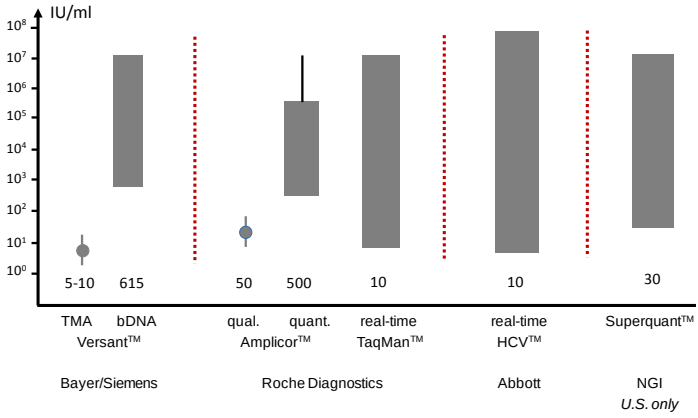

Figure 3.1 – Detection limits and linear dynamic ranges of commercially available HCV RNA detection assays.

HCV Genotyping

HCV is heterogeneous with an enormous genomic sequence variability due to its rapid replication cycle producing 10^{12} virions a day and low fidelity of the HCV RNA polymerase. Six genotypes (1-6), multiple subtypes (a, b, c...) and most recently a seventh HCV genotype have been characterized. Within one subtype, numerous quasispecies exist and may emerge during treatment with specific antivirals. Because the currently recommended treatment durations and ribavirin doses depend on the HCV genotype, HCV genotyping is mandatory in every patient considering antiviral therapy (Bowden 2006). With the new oral treatment modalities and those to come, HCV subtype determination will help to reveal possible barriers to resistance. Both direct sequence analysis and reverse hybridisation technology allow HCV genotyping.

The **Versant™ HCV Genotype 2.0 System** is suitable for indentifying genotypes 1-6 and more than 15 different subtypes and is currently the preferred assay for HCV genotyping. By simultaneous analyses of the 5'UTR and core region, a high specificity is achieved especially to differentiate the genotype 1

subtypes (1a versus 1b). The **TruGene direct sequence assay** determines the HCV genotype and subtype by direct analysis of the nucleotide sequence of the 5'UTR region. Incorrect genotyping rarely occurs with this assay. However, the accuracy of subtyping is poor. The current **RealTime™ HCV Genotype II** assay is based on real-time PCR technology, which is less time-consuming than direct sequencing. Preliminary data reveal a 96% concordance at the genotype level and a 93% concordance on the genotype 1 subtype level when compared to direct sequencing of the NS5B and 5'UTR regions.

Implications for Diagnosis and Management

Diagnosing acute hepatitis C

When acute hepatitis C is suspected, the presence of both anti-HCV antibodies and HCV RNA should be tested. For HCV RNA detection, sensitive qualitative techniques with a detection limit of 50 IU/ml or less are required, for example TMA, qualitative RT-PCR or the newly developed real-time PCR systems. HCV RNA may fluctuate during acute hepatitis C, making a second HCV RNA test necessary several weeks later in all negatively tested patients with a suspicion of acute hepatitis C. When HCV RNA is detected in seronegative patients, acute hepatitis C is very likely. When patients are positive for both anti-HCV antibodies and HCV RNA, it may be difficult to discriminate between acute and acutely exacerbated chronic hepatitis C. Anti-HCV IgM detection will not suffice because its presence is common in both situations.

Diagnosing chronic hepatitis C

Chronic hepatitis C should be considered in every patient presenting with clinical, morphological or biological signs of chronic liver disease. When chronic hepatitis C is suspected, screening for HCV antibodies by 2nd or 3rd generation EIAs is adequate because their sensitivity is >99%. When anti-HCV antibodies are detected, the presence of HCV RNA has to be

determined in order to discriminate between chronic hepatitis C and resolved HCV infection.

Diagnostics in the management of therapy

Exact HCV subtyping may gain increased importance in the future use of direct-acting antiviral agents (DAA) because some HCV subtypes behave differently regarding antiviral activity and the development of resistance. Low HCV RNA concentration (<600,000–800,000 IU/ml) at baseline is a positive predictor of a sustained virological response (SVR). Genotyping is mandatory for the selection of the optimal treatment regimen and duration of therapy, since many DAA agents are effective for only some HCV genotypes (Lange 2010), and since treatment durations generally can be shorter for patients infected with HCV genotypes 2 or 3 compared to patients infected with genotypes 1 or 4 (Manns 2006). Due to the differences in HCV RNA concentrations of up to a factor of 4 between the different commercially available assays, despite standardisation of the results to IU, and due to intra- and interassay variability of up to a factor of 2, it is recommended to always use the same assay in a given patient before, during and after treatment and to repeat HCV RNA measurements at baseline in cases with HCV RNA concentrations between 400,000 and 1,000,000 IU/ml. Furthermore, the new stopping rules for boceprevir and telaprevir triple therapies based on viral cut-offs of 100 and 1000 IU/ml respectively, were assessed by the Cobas® TaqMan® assay and no comparative data with other HCV RNA assays are available yet.

4. Hepatitis C Standard of Care

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The goal of antiviral therapy is to cure hepatitis C via a sustained elimination of the virus (2011), which is achieved if the HCV RNA remains negative six months after the end of treatment (sustained virological response, SVR) (Table 4.1). Importantly, long-term benefits of SVR are the reduction of HCV-related hepatocellular carcinoma and overall mortality (Backus 2011, Veldt 2007).

Basic therapeutic concepts and medication

The backbone of HCV treatment (Standard of Care) is pegylated interferon alfa and ribavirin. Two PEG-IFNs are available; PEG-IFN α-2b (PEG-Intron®, Merck) and PEG-IFN α-2a (PEGASYS®, Roche). Although smaller trials from southern Europe have suggested slightly higher SVR rates in patients treated with PEG-IFN α-2a (Ascione 2010, Rumi 2010), a large US multicentre study did not detect any significant difference between the two PEG-IFNs + RBV regarding SVR (McHutchison 2009b). RBV should be administered according to the bodyweight of the patient.

In 2011, the first direct antiviral agents (DAA) were approved for patients with HCV G1. Two inhibitors of the HCV protease

(PI) boceprevir (Victrelis®, Merck) and telaprevir (Incivek®, Vertex; Incivo®, Johnson & Johnson) improve SVR rates up to 75% in naïve HCV G1 patients (Jacobson 2011b, Poordad 2011b) and 29-88% in treatment experienced HCV G1 (Bacon 2011, Zeuzem 2011). However, both PIs require combination with PEG-IFN + RBV because monotherapy would result in rapid emergence of drug resistance. Both boceprevir (BOC) and telaprevir (TLV) can be combined with PEG-IFN α-2a or PEG-IFN α-2b. Approved drugs are listed in Table 4.2.

Predictors of treatment response

During the last decade, tailoring treatment duration and dosing according to individual parameters associated with response have improved SVR. Predicting SVR before the start of antiviral treatment helps in making treatment decisions. Important baseline factors associated with SVR to PEG-IFN/RBV are the HCV genotype, the degree of liver fibrosis and steatosis, baseline viral load, presence of insulin resistance, age, gender, body mass index, ethnicity, and HIV coinfection (Berg 2011, McHutchison 2009b). Many of these factors may have less relevance for triple therapy, i.e., insulin resistance seems not to impact SVR to PEG-IFN/RBV/PI (Berg 2011, Serfaty 2010) whereas low-density lipoprotein (LDL) was associated with SVR (at least for TLV) (Berg 2011).

On the other hand new parameters seem to be more important, such as HCV subtype 1a and 1b. Patients with HCV G1a have a higher risk of developing resistance during PI-based therapy compared to HCV G1b because HCV G1a requires an exchange of only one nucleotide versus two for HCV G1b in position 155 to develop resistance (reviewed in Sarrazin and Zeuzem 2010b).

Table 4.1 – Relevant definitions for HCV treatment.

	Term	Description
SVR	Sustained Virological Response	HCV RNA negative 6 months after the end of therapy
SVR-12	Sustained Virological Response	HCV RNA negative 12 weeks after the end of therapy; FDA-accepted endpoint for future trials
RVR	Rapid Virological Response	HCV RNA negative after 4 weeks of therapy
eRVR (BOC)	Extended Rapid Virological Response (for boceprevir)	HCV RNA negative (LLD not LLQ) between week 8 and week 24 of BOC therapy: RGT criterion for BOC
eRVR (TLV)	Extended Rapid Virological Response (for telaprevir)	HCV RNA negative (LLD not LLQ) between week 4 and week 12 of TLV therapy: RGT criterion for TLV
EVR	Early Virological Response	HCV RNA decline ≥2 $\log_{10}$ at week 12
cEVR	Complete Early Virological Response	HCV RNA negative at week 12
NR (BOC)	Nonresponse (boceprevir)	HCV RNA ≥100 IU/mL at week 12; or HCV RNA positive at week 24; futility rule for BOC
NR (TLV)	Nonresponse (telaprevir)	HCV RNA ≥1000 IU/mL at week 4 or week 12; or HCV RNA positive at week 12: Futility rule for TLV
BT	Breakthrough	HCV RNA was LLD but increased to ≥100 IU/mL or increase of HCV RNA ≥1 $\log_{10}$ during therapy
RL	Relapse	HCV RNA negative at EOT and recurrence of HCV RNA during the follow-up of 6 months.
PR	Partial Response	HCV RNA decline ≥2 $\log_{10}$ at week 12 but positive at week 24 during PEG-IFN/RBV
NULR	Null response	HCV RNA decline <2 $\log_{10}$ at week 12 during PEG-IFN/RBV
LI	Lead-In	4 weeks PEG-IFN/RBV before adding a PI

LLD, lower limit of detection (<10-15 IU/mL; here indicated as negative); LLQ, lower limit of quantification; EOT, end of treatment; RGT, response-guided therapy

Table 4.2 – Approved drugs for the treatment of chronic hepatitis C (2011).

Medication	Dosing
Type I interferons	Subcutaneous injection
Pegylated Interferon α-2a (Pegasys®)	180 µg once weekly
Pegylated Interferon α-2b (PEG-Intron®)	1.5 µg/kg once weekly
Interferon α-2a (Roferon®)	3 - 4.5 Mill I.U. three times weekly
Interferon α-2b (Intron A®)	3 Mill I.U. three times weekly
Consensus Interferon (Infergen®)	9 µg three times weekly
Ribavirin	Oral tablets or capsules
Ribavirin (Copegus®)	800 - 1200 mg daily (200 mg or 400 mg tablets)
Ribavirin (Rebetol®)	600 - 1400 mg daily (200 mg capsules or solution)
HCV protease inhibitors	Oral tablets or capsules
Boceprevir (Victrelis®)	800 mg (4 x 200 mg capsules) every 7-9 hours
Telapravir (Incivek®, Incivo®)	750 mg (2 x 375 mg tablets) every 7-9 hours

During treatment, the kinetics of the HCV RNA decline is a strong predictor of response. HCV RNA measurements at week 4, 12 and 24 are important for a response-guided treatment approach for PEG-IFN/RBV but also for the new triple therapy including BOC and TLV. Definitions of response and futility rules are summarized in Table 4.1. (Futility rules means that if at these time points, the viral load threshold is exceeded or detected in serum, therapy should be stopped.)

Recently, genome-wide association studies have identified host genetic polymorphisms (i.e., rs12979860, rs8099917) located on chromosome 19 located upstream to the region coding for IL28B (or IFN λ3) associated with SVR to treatment with PEG-IFN/RBV in HCV G1 patients (Ge 2009, Rauch 2010, Suppiah 2009, Tanaka 2009) but also to a lesser extent for HCV G2/3 (Mangia 2010, Sarrazin 2011b). Data on IL28B explain the different responses to PEG-IFN/RBV between different ethnic groups. However, the

negative predictive value is not strong enough to recommend general testing (EASL 2011). Viral kinetics, especially response at week 4, have a higher predictive value (Sarrazin 2011a) and the relevance of IL28B as a predictive marker for the success of triple therapy with PEG-IFN/RBV/PI is less significant (Jacobson 2011a, Pol 2011a, Poordad 2011a). However, IL28B testing may be useful to determine the IFN responsiveness and the likelihood of achieving RVR with PEG-IFN/RBV before starting triple therapy. It may be of relevance to discuss treatment options with the individual patient (see below).

Antiviral resistance

The development of direct antiviral agents leads to the emerging problem of drug resistance due to so-called resistant-associated amino acid variants (RAVs) of the virus. Patients who received monotherapy with BOC or TLV develop resistance within a few days (Sarrazin 2007). Due to their overlapping resistance profiles, one PI cannot substitute the other in the case of viral breakthrough. Also, a combination of the two PIs is not rational. PEG-IFN/RBV is mandatory for the usage of BOC or TLV and RAVs to BOC and TLV have not been associated with less sensitivity to PEG-IFN/RBV (Kieffer 2007). Importantly, if patients have a decreased PEG-IFN/RBV response, the risk of developing significant RAVs is higher. Measures for the prevention of drug resistance are adherence to the dose of the medications (most importantly to the PI) and compliance with the futility rules (see below). If RAVs emerge, it is not completely known for how long they persist and if this has any significant consequences for future therapies. Some studies suggest that the majority of resistant variants revert to wild type 1-2 years after the end of therapy (Sarrazin 2007, Sherman 2011b).

Treatment of HCV genotype 1

Treatment of naïve patients

Untreated patients with HCV genotype 1 (HCV G1) have various treatment options. Triple therapy with PEG-IFN+RBV+PI increases the overall SVR by 25-31% (Table 4.3). Many patients qualify for response-guided therapy (RGT) based on viral kinetics. In 44-65% of patients with eRVR treatment duration can be reduced to 24-28 weeks (Figures 4.1A, 4.1B), some 4-6 times more than with PEG-IFN/RBV. However, in patients with favourable predictors for SVR (low baseline HCV RNA, IL28CC, no advanced fibrosis), dual therapy with PEG-IFN/RBV may still be an option. In those patients, a lead-in of 4 weeks PEG-IFN/RBV can identify patients with RVR who achieve high SVR without adding a PI. Patients with low viral load at baseline who achieve RVR have demonstrated 78-100% SVR with 24 weeks PEG-IFN/RBV dual therapy alone (Berg 2009, Ferenci 2008, Jensen 2006, Sarrazin 2011a, Zeuzem 2006). Not adding BOC or TLV will reduce costs and adverse events, two factors that can lead to treatment discontinuation. The number of patients who qualify for dual therapy may vary depending on the distribution of IL28B polymorphisms. On the other hand, a lead-in therapy may identify patients with a poor response to IFN with a high chance of developing resistance. Only 29-31% of patients who have <1 $\log_{10}$ reduction of HCV RNA after 4 weeks PEG-IFN/RBV go on to achieve SVR when they add BOC. Other negative predictors (HCV G1a, cirrhosis) together with the lead-in concept may increase the negative predictive value of achieving SVR. In that case a wait-and-see strategy may be considered. The 4-week lead-in strategy also proved useful in assessing compliance, tolerability and safety before initiating the PI.

Table 4.3 – Phase III studies with BOC or TLV treatment regimens in treatment naïve patients with HCV genotype 1. Studies are no head-to-head studies and SVR between different studies are difficult to compare because they had significant differences in genetic and socioeconomic backgrounds.

Study	Dosing	eRVR, SVR
SPRINT-2 (Poordad 2011b) N=938 nonblack (NB) N=159 black *28 weeks if eRVR BOC	a) 1.5 µg/kg PEG-IFN a-2b, 600-1400 mg RBV 48 weeks 44 weeks Placebo (wk 4-48)	a) eRVR: 40/363 (11%) / NB: 12% SVR: 137/363 (38%) / NB: 40%
	b) 1.5 µg/kg PEG-IFN a-2b, 600-1400 mg RBV 28*-48 weeks 24 weeks 800 mg tid BOC (wk 4-28)	b) eRVR: 156/368 (42%) / NB: 45% SVR: 233/368 (63%) / NB: 67%
	c) 1.5 µg/kg PEG-IFN a-2b, 600-1400 mg RBV 48 weeks 44 weeks 800 mg tid BOC (wk 4-48)	c) eRVR: 155/366 (42%) / NB: 44% SVR: 242/366 (66%) / NB: 68%
ADVANCE (Jacobson 2011b) N=1088 *24 weeks if eRVR TLV	a) 180 µg PEG-IFN a-2a, 1000-1200 mg RBV 24*-48 weeks, 12 weeks 750 mg tid TLV (wk 0-12) *(T12PR)*	a) eRVR: 210/363 (58%) SVR: 271/363 (75%)**
	b) 180 µg PEG-IFN a-2a, 1000-1200 mg RBV 24*-48 weeks, 8 weeks 750 mg tid TLV, 4 weeks Placebo (wk 0-12)	b) eRVR: 207/363 (57%) SVR: 250/364 (69%)
	c) 180 µg PEG-IFN a-2a, 1000-1200 mg RBV 48 weeks, 12 weeks Placebo (wk 0-12)	c) SVR: 158/361 (44%)
ILLUMINATE (Sherman 2011a) N=540 N=352 (65%) eRVR N=322 randomised	a) eRVR: 180 µg PEG-IFN a2-a, 1000-1200 mg RBV 24 weeks, 12 weeks 750 mg tid TLV (wk 0-12)	a) SVR: 149/162 (92%)
	b) eRVR: 180 µg PEG-IFN a2-a, 1000-1200 mg RBV 48 weeks, 12 weeks 750 mg tid TLV (wk 0-12)	b) SVR: 140/160 (88%)
	c) no eRVR: 180 µg PEG-IFN a2-a, 1000-1200 mg RBV 48 weeks, 12 weeks 750 mg tid TLV (wk 0-12)	c) SVR: 76/118 (64%)

** numbers from the published data are different from the numbers accepted by the FDA, i.e., 79% SVR for telaprevir 12 weeks, PEG-IFN/RBV

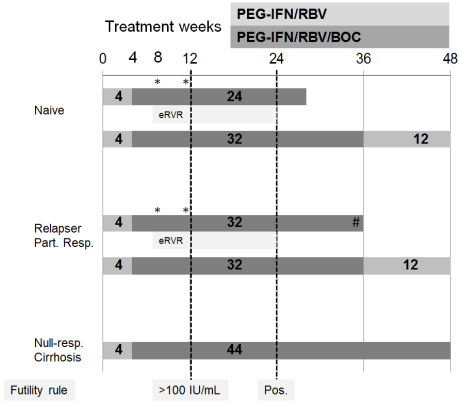

Figure 4.1A – Treatment with BOC/PEG-IFN/RBV: Approved treatment algorithm for HCV G1 patients. *, RGT if eRVR (HCV RNA LLD week 8-24); #, EMA did not approve RGT for BOC regimens in previously treated patients.

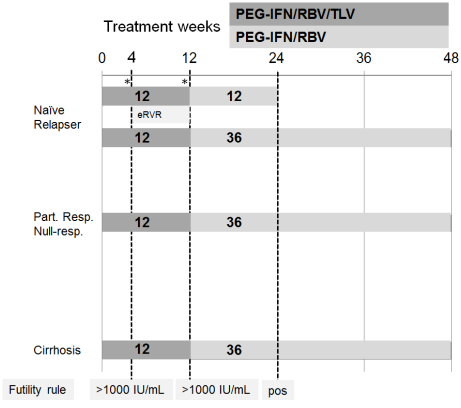

Figure 4.1B – Treatment with TLV/PEG-IFN/RBV: Approved treatment algorithm for HCV G1 patients. *RGT if eRVR (HCV RNA LLD week 4-12).

*** If patients have contraindications for BOC or TLV, dual therapy with PEG-IFN/RBV should be given for 24-72 weeks according to the HCV RNA decline at week 4 and week 12 (Sarrazin, Berg, Cornberg 2010 S3-Leitlinie). The treatment algorithm is similar to Figure 4.5.

Treatment regimens with boceprevir

800 mg BOC is given as 200 mg capsules every 7-9 hours together with food in combination with the optimal dose of PEG-IFN/RBV (Table 4.2). In all Phase III trials BOC was added after the 4-week lead-in period as described above. In SPRINT-2 (serine protease inhibitor therapy 2), the Phase III study with 1097 treatment-naïve HCV G1 patients, safety and efficacy of two regimens of BOC added to PEG-IFN α-2b/RBV after a 4-week lead-in with PEG-IFN/RBV were compared to PEG-IFN/RBV/placebo (Table 4.3) for 44 weeks. The two groups receiving BOC were treated with an RGT concept or a fixed duration of BOC. Patients in the RGT group received 24 weeks triple combination after the lead-in period. Treatment with PEG-IFN/RBV was continued through week 48 only if the criteria for eRVR were not met (HCV RNA levels undetectable from week 8 through week 24). Patients in the fixed therapy duration group received PEG-IFN/RBV/BOC for 44 weeks following the 4-week lead-in phase. Overall, adding BOC to PEG-IFN/RBV could significantly improve SVR in previously untreated patients with HCV genotype 1 leading to approval in 2011 (FDA: May; EMA: July).

The responsiveness to PEG-IFN/RBV is very important for the success of treatment with BOC. This is emphasized by the fact that the HCV RNA decline at week 4 is highly predictive of SVR. Patients with more than 1 $\log_{10}$ HCV RNA decrease after the 4-week lead-in phase demonstrated an SVR of about 80% if treated with BOC although only 28-38% responded if HCV RNA declined less than 1 $\log_{10}$. Thus, the lead-in phase can be valuable to predict the responsiveness to PEG-IFN/RBV for further individualization of therapy as discussed above. Importantly, the overall SVR rates between the RGT group and the fixed 48-week therapy group were comparable (Table 4.3). Patients achieving eRVR were eligible for a 28-week total therapy duration and almost all patients (96%) went on to achieve SVR (Poordad 2011b). Of note, HCV RNA negative means below the limit of detection (LLD) and not below limit of quantification (LLQ). This is important because SVR is diminished in patients with LLQ at

weeks 8-24 who were treated for a shorter duration (Harrington 2011).

FDA and EMA have approved RGT for treatment-naïve patients except for patients with liver cirrhosis (Figure 4.1A) but the accepted treatment duration for BOC based on RGT is different to the study design of the Phase III study (32 vs 24 weeks BOC for patients without eRVR) (Figure 4.1A). In addition, a retrospective analysis led to the futility rule of HCV RNA >100 IU/mL at week 12. The predictive value for nonresponse was 100%. BOC was initially combined with PEG-IFN α-2b. Recently, a study in therapy-experienced patients including relapsers and partial responders showed similar results with PEG-IFN a-2a/RBV (Flamm 2011). Thus, both PEG-IFNs can be combined with BOC.

Treatment regimens with telaprevir

750 mg TLV given as 375 mg tablets every 7-9 hours together with food (ideally >20 g fat) requires combination with optimal PEG-IFN/RBV. Telaprevir was administered for a maximum of 12 weeks in the Phase III trials; longer treatment duration is associated with increasing adverse events (McHutchison 2010). Two large Phase III studies (ADVANCE and ILLUMINATE) with a total of 1628 treatment-naïve HCV G1 patients showed that PEG-IFN/RBV/TLV significantly improved SVR compared to PEG-IFN/RBV and RGT is possible (Jacobson 2011b, Sherman 2011a). TLV was approved for the treatment of HCV G1 in 2011 (FDA: May; EMA: September). In the ADVANCE trial, 3 treatment groups were assessed for efficacy and safety using RGT in treatment-naïve patients (Jacobson 2011b). 12 weeks of TLV versus 8 weeks of TLV in combination with 24-48 weeks PEG-IFN/RBV were compared to 48 weeks PEG-IFN/RBV dual therapy. Patients who achieved eRVR qualified for 24 weeks of therapy (Table 4.3). SVR was significantly higher among those receiving TLV compared to the placebo group; 12 weeks TLV resulted in the highest SVR (Table 4.3). In all treatment groups, more than

80% of patients who achieved eRVR had SVR (89%, 83%, and 97%, respectively) (Jacobson 2011b).

To validate RGT, telaprevir 750 mg every 8 hours for 12 weeks was evaluated in an open-label study (ILLUMINATE trial) to prospectively assess 24 vs 48 weeks of treatment for HCV G1 patients who achieved eRVR. If HCV RNA levels were undetectable at weeks 4 and 12, patients were randomly assigned to continue with PEG-IFN/RBV for an additional 24 or 48 weeks. If eRVR was not attained, patients received PEG-IFN/RBV for up to 48 weeks. Of the 540 subjects, 389 (72%) achieved HCV RNA levels LLD at week 4 and 352 (65%) achieved eRVR. Patients who achieved eRVR and were randomized to the 24-week cohort experienced 92% SVR versus 88% who were treated for 48 weeks (Table 4.3) (Sherman 2011a). Importantly, patients with liver cirrhosis showed higher relapse rates with shorter treatment, therefore RGT for TLV has only been approved for naïve HCV G1 patients without liver cirrhosis. Also, retrospective analysis of the data showed that early HCV RNA measurement at week 4 is predictive of nonresponse to TLV. Patients with HCV RNA values >1000 IU/mL after 4 weeks PEG-IFN/RBV/TLV did not achieve SVR. Therefore, therapy must be stopped.

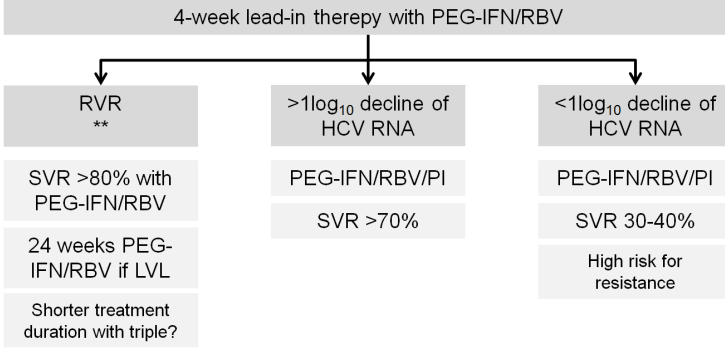

Figure 4.2 – Suggestion to use the lead-in strategy for individualisation of treatment in patients with HCV genotype 1. **The number of patients with low baseline HCV RNA and RVR may vary between different countries due to IL28B differences.

Treatment of patients with prior antiviral treatment failure

Definition of treatment failure

Definition of response to or failure on antiviral therapy is very important when considering retreating patients with chronic hepatitis C because the success of BOC- or TLV-based regimens depends on the IFN responsiveness. Patients may have been treated with different treatment regimens and compliance during the previous therapy was probably very varied. Most importantly, HCV RNA kinetics and the response profile during the previous therapy have to be taken into account before starting a new treatment. It is crucial to screen the patient's records and check treatment duration, drug dosing and HCV RNA of the previous therapy. Non-response is the failure of a patient to clear HCV RNA at any point during treatment. Definitions used for trials assessing novel therapy approaches have generally defined non-response as the failure to achieve EVR, which is ≥2 $\log_{10}$ reduction of HCV RNA after 12 weeks. Classifications of non-response include null response, partial-response, relapse, and breakthrough.

Retreatment of HCV G1 patients with relapse after PEG-IFN/RBV

Retreatment with PEG-IFN/RBV of relapse patients after IFN- or PEG-IFN-based combination therapy with ribavirin resulted in an SVR of 24-34% (Bacon 2011, Poynard 2009, Zeuzem 2011). Triple therapy with PEG-IFN/RBV/PI increases SVR dramatically, to 69-88% (Bacon 2011, Zeuzem 2011) (Table 4.4). Relapse patients are the ideal patients for retreatment with a triple therapy regimen. Patients have already proven to respond to PEG-IFN and RBV. Thus, the backbone to prevent PI resistance is effective and a lead-in strategy may not be as important as in other situations. Although RGT was not evaluated in the Phase III REALIZE trial with TLV, a rollover study including relapse patients from Phase II studies has demonstrated that shorter treatment is effective in patients with eRVR (Muir 2011). Therefore, RGT is possible with

BOC and TLV regimes (Figures 4.1A, 4.1B) if cirrhosis is excluded (Ghany 2011, Sarrazin 2012). However, BOC RGT has only been approved by the FDA and not by the EMA because SVR was slightly lower in the RESPOND-2 RGT group (Table 4.4).

Retreatment of HCV G1 patients with partial response to PEG-IFN/RBV

Patients who are partial-responders (PR) to standard PEG-IFN/RBV combination therapy have demonstrated SVRs ranging between 7% and 15% with a standard PEG-IFN/RBV retreatment (Bacon 2011, Zeuzem 2011). Retreatment with triple therapy increases SVR to 40%-59% (Bacon 2011, Zeuzem 2011) (Table 4.4). FDA but not EMA approved RGT for BOC (Figures 4.1A, 4.1B). Treatment duration for PEG-IFN/RBV/TLV is 48 weeks for all PR patients (Figure 4.1B). The 4-7-fold increase justifies retreatment. However, SVR decreases significantly in patients with cirrhosis (34% with TLV) and other negative response factors (Pol 2011b).

Retreatment of HCV G1 patients with null response to PEG-IFN/RBV

Patients who are null responders (NULR) to standard PEG-IFN/RBV combination therapy have demonstrated SVRs ranging between 5% and 16% with an optimised PEG-IFN/RBV retreatment (Jensen 2009, Poynard 2009, Zeuzem 2011). Retreatment with PEG-IFN/RBV/PI did increase SVR more than 6-fold in the REALIZE trial (Zeuzem 2011). However, overall SVR with triple therapy is limited to 29-38% (Vierling 2011, Zeuzem 2011) (Table 4.4). If further negative predictive factors are present, SVR decreases to 27% in HCV G1a patients and to 14% in cirrhotic patients (not significantly different from PEG-IFN/RBV) (Figure 4.6A). This may justify the lead-in concept to decide if treatment with a PI is beneficial. Patients who do not acheive a 1 $\log_{10}$ decline of HCV RNA after 4 weeks demonstrate only 15% SVR (Zeuzem 2011). Futility rules are the same for treatment-experienced patients as for treatment-naïve patients (Figures 4.1A, 4.1B).

Table 4.4 – Phase III studies with BOC or TLV treatment regimens in treatment-experienced patients infected with HCV genotype 1. Studies are not head-to-head and SVR between studies are difficult to compare because they had significant differences in genetic and socioeconomic backgrounds.

Study	Dosing	SVR
RESPOND-2 (Bacon 2011) n=403 *36 weeks if eRVR BOC	a) 1.5 µg/kg PEG-IFN a-2b, 600-1400 mg RBV 48 weeks 44 weeks Placebo (wk 4-48)	a) All: 21% REL: 29% PR: 7%
	b) 1.5 µg/kg PEG-IFN a-2b, 600-1400 mg RBV 36*-48 weeks 32 weeks 800 mg tid BOC (wk 4-36)	b) All: 59% REL: 69% PR: 40%
	c) 1.5 µg/kg PEG-IFN a-2b, 600-1400 mg RBV 48 weeks 44 weeks 800 mg tid BOC (wk 4-48)	c) All: 66% REL: 75% PR: 52%
(Flamm 2011) n=201	a) 180 µg PEG-IFN a-2a, 1000-1200 mg RBV 48 weeks 44 weeks Placebo (wk 4-48)	a) REL, PR: 21%
	b) 180 µg PEG-IFN a-2a, 1000-1200 mg RBV 48 weeks 44 weeks 800 mg tid BOC (wk 4-48)	b) REL, PR: 64%
PROVIDE (Vierling 2011) n=48 (42 available)	1.5 µg/kg PEG-IFN a-2b, 600-1400 mg RBV 48 weeks 44 weeks 800 mg tid BOC (wk 4-48)	38% (16/42)
REALIZE (Zeuzem 2011) n=663	a) 180 µg PEG-IFN a-2a, 1000-1200 mg RBV 48 weeks, 12 weeks Placebo (wk 0-12)	a) REL: 24% PR: 15% NULR: 5%
	b) 180 µg PEG-IFN a-2a, 1000-1200 mg RBV 48 weeks, 4 weeks Placebo (wk 0-4), 12 weeks 750 mg tid TLV (wk 4-16) → Lead-in cohort	b) REL: 88% PR: 54% NULR: 33%
	c) 180 µg PEG-IFN a-2a, 1000-1200 mg RBV 48 weeks, 12 weeks 750 mg tid TLV (wk 0-12), 4 weeks Placebo (wk 12-16),	c) REL: 83% PR: 59% NULR: 29%

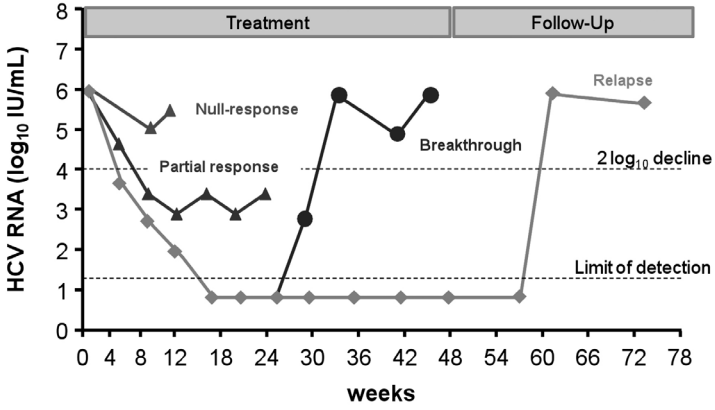

Figure 4.3 – Different scenarios of treatment failure to antiviral therapy in chronic hepatitis C.

Treatment of HCV genotypes 2 and 3

Naïve patients

TLV shows antiviral efficacy against HCV G2 but is not effective against HCV G3 (Foster 2011). Data for BOC have only been presented in abstract form for 400 mg TID in a small number of patients (Silva 2011). Importantly, both PIs are approved only for the treatment of HCV G1. Thus, SOC for HCV G2/3 infection remains the combination of PEG-IFN/RBV. Although a fixed duration of treatment (24 weeks) has been advocated, the optimal results are likely to be achieved when the duration of therapy is adjusted based on viral kinetics. Many studies have investigated the reduction of treatment duration for HCV G2/3 to 16, 14, or even 12 weeks. Overall, reducing the treatment duration to less than 24 weeks increases the number of relapses (Andriulli 2008, Dalgard 2008, Mangia 2005, Manns 2011a, Shiffman 2007b). However, some HCV G2/3 patients may indeed be treatable for 12-16 weeks if certain prerequisites are fulfilled, especially RVR by week 4 of therapy (Slavenburg 2009). Only patients with RVR have high SVR rates after 16 weeks (Manns

2011a, von Wagner 2005), 14 weeks (Dalgard 2008), or even 12 weeks of therapy (Mangia 2005).

In addition to the RVR, the specific HCV genotype and the baseline viral load are associated with response. Patients with HCV G2 respond better to PEG-IFN/RBV therapy than those infected with HCV G3 (Zeuzem 2004b). Furthermore, the shorter treatment schedules reveal that HCV G3 patients with low baseline viremia (<400-800.000 IU/ml) had a much better chance of responding than those with high viral load (>400-800,000 IU/ml) (Shiffman 2007b, von Wagner 2005). Patients with HCV G3 plus low viral load who achieve RVR can be treated for less than 24 weeks. However, reducing treatment duration is not recommended in patients with advanced liver fibrosis or cirrhosis, insulin resistance, diabetes mellitus, hepatic steatosis or BMI >30 kg/m^2 (Aghemo 2006, Sarrazin 2010a, Sarrazin 2011). Patients treated with a response-guided approach should be started on high-dose ribavirin, which appears to increase the rate of RVR in patients with HCV G2/3 undergoing short treatment (Mangia 2010b).

In contrast, HCV G2/3 patients who do not achieve RVR (especially HCV G3 and high viral load) may be treated for longer than 24 weeks (i.e., 36-48 weeks) (Figure 4.4).

Treatment of HCV G2/3 patients with prior antiviral treatment failure

Patients with relapse after a short course of PEG-IFN/RBV show adequate SVR after retreatment for 24 weeks (Mangia 2009). In patients with unfavourable predictors, longer treatment duration for 48 weeks is advisable **(**EASL 2011**)**. Nonresponders can be retreated with an additional course of PEG-IFN/RBV. It is important to optimise dose and duration of treatment. HCV G2 nonresponders may benefit from retreatment with PEG-IFN/RBV/PI (so far, only for TLV). Triple therapy is off-label but may be considered in difficult-to-treat HCV G2 patients with an urgent treatment indication. Future DAAs will be pan-genotypic and therefore also effective for HCV G3. Nonresponder patients

with mild fibrosis may therefore wait for new treatment options, but it is important to understand that fibrosis progression is faster in patients with HCV G3 (Bochud 2009).

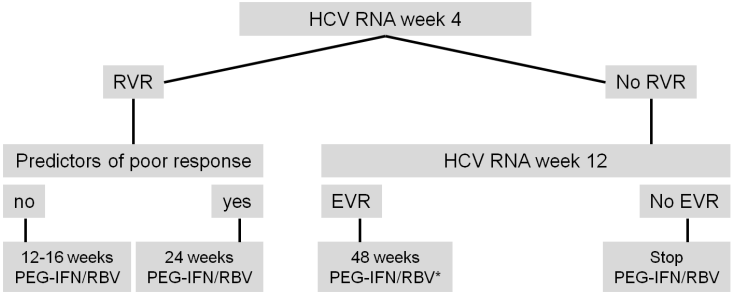

Figure 4.4 – Recommendation for treatment of HCV genotypes 2 and 3. Sensitive HCV RNA assays (limit of detection 12-15 IU/ml or 50 IU/ml) at weeks 4 and 12 may determine treatment duration. Reducing treatment duration is not recommended in patients with liver cirrhosis, insulin resistance, diabetes mellitus or hepatic steatosis.

Treatment of HCV genotypes 4, 5, and 6

BOC and TLV have hardly been tested in patients with HCV G4, 5, or 6. Neither PI is approved for the treatment of HCV G4, 5, or 6. Thus, SOC remains the combination of PEG-IFN/RBV. In general, treatment duration of 48 weeks is recommended based on the results of the large, randomized Phase III trials (Fried 2002, Hadziyannis 2004, Manns 2001). However, these trials included few patients with HCV G4, 5, and 6 and further large, prospective randomized studies with RGT are rare. Importantly, HCV G4, 5, and 6 are very common in areas where chronic hepatitis C is highly prevalent.

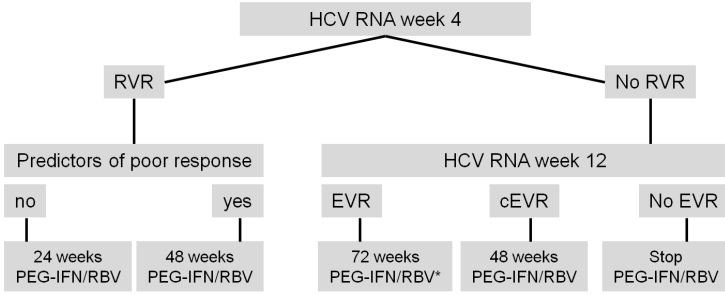

Figure 4.5 – Suggestion for treatment of HCV genotypes 4, 5, and 6. This algorithm was initially proposed for HCV G4 (adapted Khattab 2011). Sensitive HCV RNA assays (limit of detection 12-15 IU/ml or 50 IU/ml) at weeks 4 and 12 may determine treatment duration. Reducing treatment duration is not recommended in patients with predictors of poor response (liver cirrhosis, insulin resistance, diabetes mellitus or hepatic steatosis, high baseline viral load >800,000 IU/mL).

The available study results, although limited, suggest that patients with HCV G4, 5 and 6 may show different clinical courses and treatment outcomes. Ethnicity-related factors (i.e., IL28B, regional aspects) may contribute to these findings. Overall, data from smaller studies suggest that HCV G4, 5 and 6 appear easier-to-treat compared to HCV G1 but the optimal treatment duration is not clear (Antaki 2010, Nguyen 2005).

Optimisation of HCV treatment

Adherence to therapy

Adherence to therapy is one of the most important factors associated with the success of antiviral treatment (McHutchison 2002). For the new triple therapy, adherence to the PI becomes even more important as mentioned above. The three-times-daily regimen necessitates highly motivated patients. BOC and TLV have to be taken every 7-9 hours together with food. Reduction of the PI or irregular intake bears the risk for rapid emergence of drug resistance. Dose reduction of the PI is associated with

significantly diminished SVR (Gordon 2011) and is therefore not an option to manage side effects. An optimal management of PEG-IFN/RBV side effects therefore is essential in order to optimise treatment responses. In the case of anemia, dose reduction of ribavirin is possible and not associated with impaired SVR to triple therapy (Roberts 2011). Another important and new issue is drug interactions that can diminish the effectiveness of the PI or induce toxicity of concomitant medications, which may lead to discontinuation of all drugs. Knowledge about drug interactions is therefore important for the optimal management of patients receiving PEG-IFN/RBV/PI.

Management of side effects and complications

Severe side effects may reduce adherence to therapy and may result in dose modifications that result in a less-than-optimal response. IFN, ribavirin and the new protease inhibitors induce side effects that have to be managed with the patient (Table 4.5). For detailed information, see Chapter 6.

Table 4.5 – Common side effects (>5% of patients) recorded in the PEG-IFN/RBV/PI trials. The incidence of side effects between different studies is difficult to compare because there were significant differences in genetic and socioeconomic backgrounds. There were methodological differences in assessing side effects as well. Patients were selected on the basis of well-defined inclusion and exclusion criteria. Important differences between PEG-IFN/RBV and PEG-IFN/RBV/PI are highlighted in bold.

Side effects	Incidence with PEG-IFN/RBV	Incidence with PEG-IFN/RBV/BOC	Incidence with PEG-IFN/RBV/TLV
Fatigue	50%†, 57%*	57%*	56%†
Insomnia	31%‡,*	32%*	32%‡
Headache	39%‡, 43%*	44%*	41%-43%‡
Pyrexia	24%‡, 31%*	31%*	26%-30%‡
Nausea	31%‡, 40%*	45%*	40-43%‡
Diarrhea	17%†, 18%*	23%*	26%†
Alopecia	25%*	26%*	n.a.
Depression	20%*	20%*	No difference‡
Anemia	17%†, 29% §,*	49%§*	36%†
Neutropenia	18%*,**	23%*	23%**
Dysgeusia	3%†, 15%*	37%*	10%†
Rash	17%*, 34%†	16%*	56%†
Pruritus	23%*, 28%†	21%*	47%†
Anorectal discomfort	1%*, 3%†	1%*	11%†
Anal pruritus	1%†	n.a.	6%†
Hemorrhoids	3%*,†	4%*	12%†

* Manns 2011b, † Vertex 2011, ‡ Jacobson 2011b, § EPO was allowed,
** Zeuzem 2011

Drug interactions

BOC and TLV undergo extensive hepatic metabolism especially by the cytochrome P450 CYP3A pathway. Thus, both PIs are target as well as perpetrator of drug interactions. As inhibitors

of CYP3A, both PIs can result in increased plasma concentrations of concomitant drugs that are metabolized via the same route, leading to prolonged therapeutic effects and/or toxicity. In contrast, concomitant drugs that induce CYP3A may result in decreased plasma concentrations of BOC or TLV, which can reduce the therapeutic effect. TLV is also an inhibitor of PGP transport. Coadministration of TLV with drugs that are substrates for PGP transport may result in increased plasma concentrations of such drugs, which could increase adverse reactions. Based on *in vitro* experiments BOC also has the potential to inhibit PGP. Importantly, BOC is metabolized not only by cytochrome P450-mediated oxidation but also significantly by ketone reduction via aldo-keto reductase (AKR). Because the biotransformation and clearance of BOC involves two different enzymatic pathways, drug interactions with BOC may be less likely compared to TLV. For the optimal management of triple therapy, it is essential to specifically ask patients about concomitant medications and investigate if those drugs may interact with the PI. Even herbals and food have to be considered as St. John's Wort is a potent inducer of CYP3A and naringin, an ingredient of grapefruit, an inhibitor. A list of drug interactions is given in the prescribing information. Supportive online tools or apps for mobile devices are available. One example is the comprehensive drug interaction resource provided by the University of Liverpool (http://www.hep-druginteractions.org). The website provides clinically useful and evidence-based information which is updated when new drug interactions are analysed and published. Drug interactions are considered significant if the area under the plasma concentration time curve (AUC) is changed by more than 30%.

Treatment of hepatitis C in special populations

Patients with acute hepatitis C

The immediate treatment of patients with symptomatic acute hepatitis C with recombinant IFN or PEG-IFN monotherapy for 24

weeks can prevent the development of chronic hepatitis C in approximately 90% of cases (Broers 2005, Jaeckel 2001, Santantonio 2005, Vogel 1996, Wiegand 2006). Coadministration with ribavirin does not seem to be necessary. This may be different in patients with HIV coinfection (Grebely 2011a). TLV and BOC have not been tested in patients with acute HCV infection. Symptomatic patients also have a good chance of clearing HCV spontaneously (Gerlach 2003, Hofer 2003), occurring usually in the first 12 weeks after the onset of symptoms.

As for patients with treatment-induced SVR, spontaneous clearance of HCV is also associated with IL28B polymorphisms and IP-10 (Beinhardt 2012, Grebely 2010, Thomas 2009, Tillmann 2010), which may be useful for decision-making. The treatment of only those patients who remain HCV RNA-positive 12 weeks after the onset of symptoms results in an overall SVR (self-limited and treatment-induced) in 91% of patients (Gerlach 2003). Asymptomatic patients, however, should probably be treated immediately since these patients have a higher risk for evolution to a chronic state.

Patients with compensated liver cirrhosis

Successful therapy of patients with advanced fibrosis and liver cirrhosis is associated with decreased incidence of HCC, decompensation and liver-related mortality (Morgan 2010, Veldt 2007). In addition, in patients awaiting liver transplantation, successful therapy prevents graft rejection (Everson 2005, Forns 2003). Thus, patients should be considered for therapy if no contraindications are present. However, SVR is diminished in patients with cirrhosis, for the new triple therapy as well (Pol 2011b) (Figure 4.6A, 4.6B).

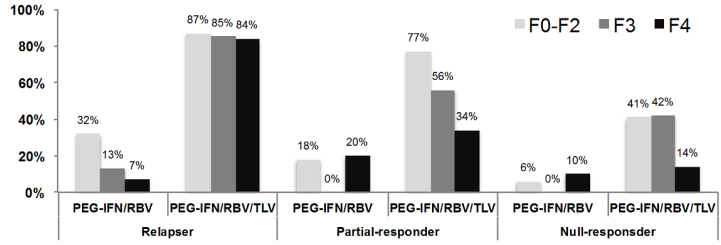

Figure 4.6A – SVR of TLV-based regimens in patients with HCV genotype 1 according to fibrosis stage. Subanaylsis of the REALIZE Phase III trial (Pol 2011b).

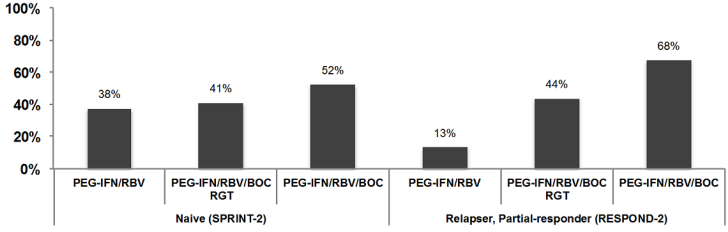

Figure 4.6B – SVR of BOC-based regimens in patients with HCV genotype 1 with advanced fibrosis and cirrhosis (F3-F4). Subanaylsis of the SPRINT-2 and RESPOND-2 trials (Bruno 2011).

Patients with liver cirrhosis must be treated for a fixed duration of 48 weeks. Thus, exposure to drugs associated with side effects is still long in the new era of PIs. Treatment of patients with liver cirrhosis requires a close monitoring of patients. Hematological adverse events are more frequent than in non-cirrhotic patients (EASL 2011). Of note, patients with advanced cirrhosis (i.e., platelets <75K/µl) have not been treated with BOC or TLV because they were excluded from the large Phase II and III studies. In general, treatment should be limited to patients with Child-Pugh A cirrhosis. In patients with Child-Pugh B cirrhosis, therapy may be only considered in individual cases in experienced centres. If ascites is present, antibiotic prophylaxis

should be given. If patients with cirrhosis achieve SVR, it is important to perform HCC surveillance because cirrhosis remains and HCC development is reduced but not abolished (EASL 2011).

Patients after liver transplantation

HCV definitely takes a more rapid course post-transplant than in immunocompetent individuals and treatment needs are obvious. BOC and TLV are currently being evaluated in patients after liver transplantation. Besides adverse events (anemia, neutropenia), drug interactions with immunosuppressive drugs need to be considered. For example, TLV increases levels of tacrolimus by approximately 70-fold (Garg 2011).

Outlook

Treatment of chronic hepatitis C is one of the success stories of modern medicine. In the first interferon trials published in 1989, interferon α three times a week achieved sustained virological responses in only a few patients. In 2011, treatment is successful in up to 80% of selected patient populations. Many issues remain to be addressed, though. Treatment is costly and not readily available for patients in areas where hepatitis C prevalence is high. Treatment is not easy, either. It often lasts 6 to 12 months and the drugs used are not always well tolerated.

Further progress is looming on the horizon. Knowledge of the molecular structure of the hepatitis C proteins has allowed the design of new drugs targeting the sites of HCV-encoded enzymes that are important for the replication of the virus. The HCV protease and polymerase are currently the main targets. Approval of the first protease inhibitors came in 2011. Even if PEG-IFN and ribavirin remain the backbone of standard therapy for the near future, the new oral drugs might transform chronic hepatitis C infection into a curable disease for a majority of patients. Further improvements may be “just around the corner”.

5. New Drugs

Christian Lange and Christoph Sarrazin

Combination therapy with pegylated interferon α plus weight-based ribavirin leads to sustained virologic response (SVR, i.e., undetectable HCV RNA 24 weeks after treatment completion) in approximately 50% of all HCV genotype 1-infected patients, compared to 70-90% of patients infected with HCV genotypes 2 and 3 (Zeuzem 2009). The limited treatment success in HCV genotype 1 patients, the long treatment durations (up to 72 weeks), the numerous side effects of PEG-IFN α and ribavirin therapy, and an exploding knowledge of the HCV life cycle and of structural features of the HCV proteins, has spurred the development of many promising directly acting antiviral agents (DAA) (Kim 1996, Lindenbach 2005, Lohmann 1999, Lorenz 2006, Wakita 2005). In principle, each of the four HCV structural and six non-structural proteins, HCV-specific RNA structures such as the IRES, as well as host factors on which HCV depends, are suitable targets for DAA agents. In the following section, DAA compounds currently in clinical development are presented (Table 5.1, Figure 5.1).

Table 5.1 – Selected directly acting antiviral agents (DAAs) in the pipeline.

Drug name	Company	Target / Active site	Phase
NS3-4A protease inhibitors			
Telaprevir (VX-950)	Vertex / Janssen	Active site / linear	IV
Boceprevir (SCH503034)	Merck (S-P)	Active site / linear	IV
Simeprevir (TMC435350)	Janssen / Medivir	Active site / macrocyclic	III
Danoprevir (R7227)	Roche / InterMune	Active site / macrocyclic	II
Vaniprevir (MK-7009)	Merck	Active site / macrocyclic	*
MK-5172	Merck	Active site / macrocyclic	II
BI201335	Boehringer Ing.	Active site / linear	III
Asunaprevir (BMS-650032)	BMS	Active site	II
PHX1766	Phenomix	Active site	I
GS-9256	Gilead	Active site	II
GS-9451	Gilead	Active site	I
ABT450	Abbott	Active site	II
IDX320	Idenix	Active site	II
ACH-1625	Achillion	Active site / macrocyclic?	II
Nucleoside analog NS5B polymerase inhibitors			
Mericitabine (R7128)	Roche / Pharmasset	Active site	II
GS-7977 (PSI-7977)	Gilead / Pharmasset	Active site	II
GS-938 (PSI-938)	Gilead / Pharmasset	Active site	II
IDX184	Idenix	Active site	II
Non-nucleoside NS5B polymerase inhibitors (NNI)			
BI207127	Boehringer Ing.	NNI site 1 / thumb 1	II
MK-3281	Merck	NNI site 1 / thumb 1	II
TMC647055	Janssen	NNI site 1 / thumb 1	
Filibuvir (PF-00868554)	Pfizer	NNI site 2 / thumb 2	II
VCH759	ViroChem Pharma	NNI site 2 / thumb 2	II
VCH916	ViroChem Pharma	NNI site 2 / thumb 2	II
VCH222	ViroChem Pharma	NNI site 2 / thumb 2	II
ANA598	Anadys	NNI site 3 / palm 1	II
ABT-072	Abbott	NNI site 3 / palm 1	II
ABT-333	Abbott	NNI site 3 / palm 1	II
GS-9190	Gilead	NNI site 4 / palm 2	II
IDX375	Idenix	NNI site 4 / palm 2	II

Drug name	Company	Target / Active site	Phase
NS5A inhibitor			
Daclatasvir (BMS-790052)	BMS	NS5A domain 1 inhibitor	II
BMS-824393	BMS	NS5A protein	I
PPI-461	Presidio Ph.	NS5A protein	I
GS-5885	Gilead	NS5A protein	I
Indirect inhibitors / unknown mechanism of action			
Alisporivir (Debio-025)	Debiopharm	Cyclophilin inhibitor	III
NIM811	Novartis	Cyclophilin inhibitor	I
SCY-635	Scynexis	Cyclophilin inhibitor	II
Nitazoxanide		PKR induction (?)	II
Miravirsen	Santaris	miRNA122 antisense RNA	II
Celgosivir	Migenix	A-glucosidase inhibitor	II

* Halted

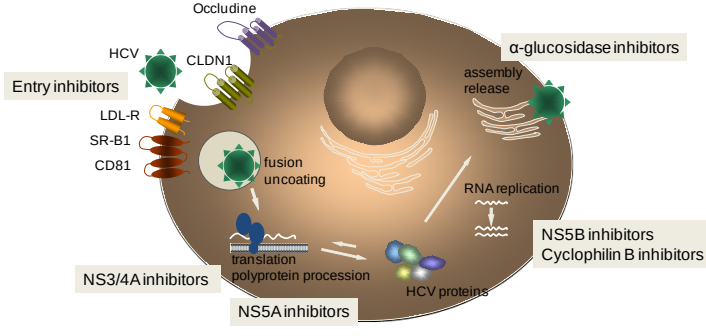

Figure 5.1 – HCV life cycle and targets for directly acting antiviral agents (DAAs).

NS3-4A protease inhibitors

Molecular biology

After receptor-mediated endocytosis, the fusion of HCV with cellular membranes and the uncoating of the viral nucleocapsid, the single-stranded positive-sense RNA genome of the virus is released into the cytoplasm to serve as a messenger RNA for the HCV polyprotein precursor. HCV mRNA translation is under the control of the internal ribosome entry site (IRES), formed by domains II-IV of the HCV 5´UTR (Moradpour 2007). IRES mediates HCV polyprotein translation by forming a stable complex with the 40S ribosomal subunit, eukaryotic initiation factors and viral proteins.

From the initially translated HCV polyprotein, the three structural and seven non-structural HCV proteins are processed by both host and viral proteases (Moradpour 2007). NS2 is a metalloproteinase that cleaves itself from the NS2/NS3 protein, leading to its own loss of function and to the release of the NS3 protein (Lorenz 2006). NS3 provides a serine protease activity and a helicase/NTPase activity. The serine protease domain comprises two b-barrels and four α-helices. The serine protease catalytic triad – histidine 57, asparagine 81 and serine 139 – is located in a small groove between the two b-barrels (Kim 1996, Kim 1998). NS3 forms a tight, non-covalent complex with its obligatory cofactor and enhancer NS4A, which is essential for proper protein folding (Figure 5.2). The NS3-4A protease cleaves the junctions between NS3/NS4A, NS4A/NS4B, NS4B/NS5A and NS5A/NS5B. Besides its essential role in protein processing, NS3 is integrated into the HCV RNA replication complex, supporting the unwinding of viral RNA by its helicase activity. Moreover, NS3 might play an important role in HCV persistence via blocking TRIF-mediated toll-like receptor signalling and Cardif-mediated RIG-I signalling, subsequently resulting in impaired induction of type I interferons (Meylan 2005). Thus, pharmacologic NS3 inhibition might support viral clearance by restoring the innate immune response.

In general, NS3-4A protease inhibitors have been shown to strongly inhibit HCV replication during monotherapy, but also can cause the selection of resistant mutants, followed by viral breakthrough. The additional administration of pegylated interferon and ribavirin, however, was shown to reduce the development of resistance. Combination therapies with different antiviral drugs can prevent the development of resistance. Telaprevir and boceprevir were both approved in 2011.

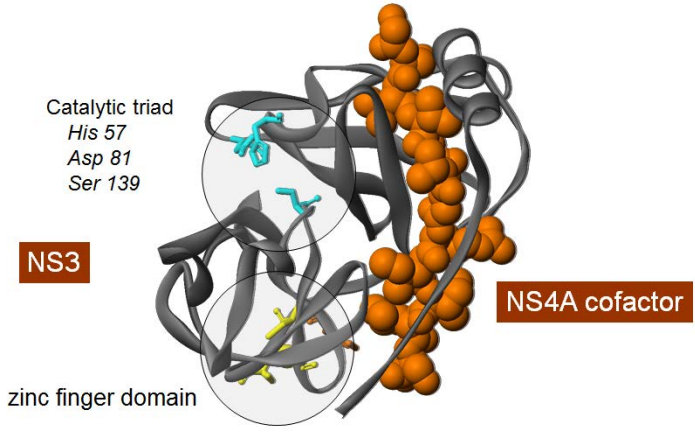

Figure 5.2 – Molecular structure of the HCV NS3-4A protease.

Telaprevir (Incivek/Incivo®) and boceprevir (Victrelis®)

Telaprevir and boceprevir were approved for the treatment of chronic hepatitis C virus genotype 1 infection by the FDA, EMA and several other agencies in 2011. Both telaprevir and boceprevir are orally bioavailable, peptidomimetic NS3-4A protease inhibitors belonging to the class of α-ketoamid derivatives. Like other NS3-4A inhibitors, telaprevir and boceprevir are characterized by a remarkable antiviral activity against HCV genotype 1. However, monotherapy with these agents results in the rapid selection of drug-resistant variants

followed by viral breakthrough (Reesink 2006, Sarrazin 2007). Phase II and III clinical studies have shown that the addition of pegylated interferon α plus ribavirin leads to a substantially reduced frequency of resistant mutants and viral breakthrough, and to significantly higher SVR rates in both treatment-naïve and treatment-experienced HCV genotype 1 patients compared to treatment with pegylated interferon α and ribavirin alone (Bacon 2011, Jacobson 2011, Poordad 2011, Sherman 2011, Zeuzem 2011). Therefore, telaprevir- and boceprevir-based triple therapy can be considered standard of care for HCV genotype 1 patients. Results of the Phase III telaprevir and boceprevir approval studies are summarized in Figure 5.3.

Other NS3 protease inhibitors

Other NS3 protease inhibitors are currently in various phases of development (Table 5.1) and will significantly increase treatment options for chronic hepatitis C in the near future. In general, comparable antiviral activities to telaprevir and boceprevir in HCV genotype 1 infected patients were observed during mono- (and triple-) therapy studies (Brainard 2010, Manns 2011, Reesink 2010). Potential advantages of these second- and third-generation protease inhibitors might be improved tolerability, broader genotypic activity, different resistance profiles, and/or improved pharmacokinetics for once-daily dosage (e.g., TMC435, BI201335). Different resistance profiles between linear tetrapeptide and macrocyclic inhibitors binding to the active site of the NS3 protease have been revealed. However, R155 is the main overlapping position for resistance and different mutations at this amino acid site within the NS3 protease confer resistance to nearly all protease inhibitors currently in advanced clinical development (Sarrazin 2010). An exception is MK-5172, which exhibits potent antiviral activity against variants carrying mutations at position R155. In addition, MK-5172 has potent antiviral activity against both HCV genotype 1 and 3 isolates (Brainard 2010).

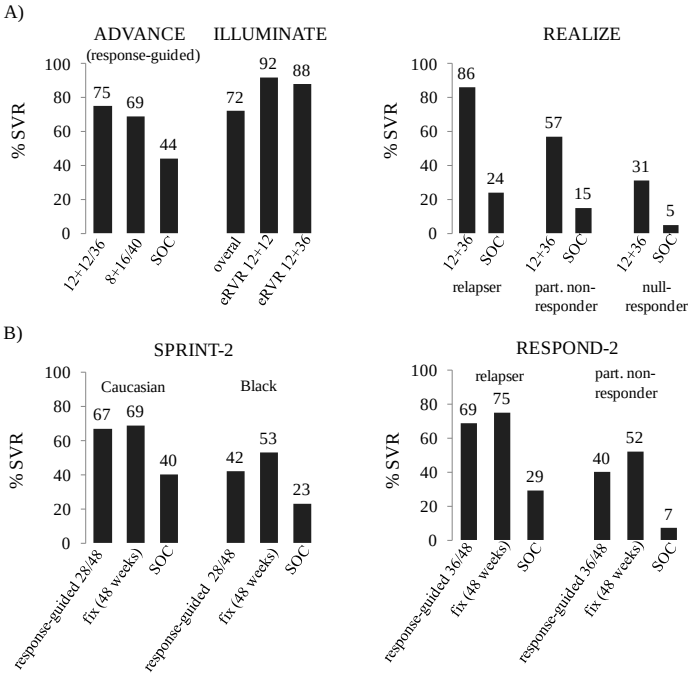

Figure 5.3 — SVR rates in Phase III clinical trials evaluating telaprevir (A) or boceprevir (B) in combination with PEG-IFN α and ribavirin. ADVANCE, ILLUMINATE and SPRINT-2 enrolled treatment-naïve patients, REALIZE and RESPOND-2 enrolled treatment-experienced patients. Telaprevir was administered for 8 or 12 weeks in combination with PEG-IFN α-2a and ribavirin, followed by 12-40 weeks of PEG-IFN α-2a and ribavirin alone. Boceprevir was administered over the whole treatment period of 28 or 48 weeks in combination with PEG-INF α-2b and ribavirin, except of the first 4 weeks of lead-in therapy of PEG-IFN α-2b and ribavirin only. eRVR, extended early virologic response; SOC, standard of care; LI, lead-in (4 weeks of PEG-INF α plus ribavirin only).

Resistance to NS3-4A inhibitors

Because of the high replication rate of HCV and the poor fidelity of its RNA-dependent RNA polymerase, numerous variants (quasispecies) are continuously produced during HCV

replication. Among them, variants carrying mutations altering the conformation of the binding sites of DAA compounds can develop. During treatment with specific antivirals, these preexisting drug-resistant variants have a fitness advantage and can be selected to become the dominant viral quasispecies. Many of these resistant mutants exhibit an attenuated replication with the consequence that, after termination of exposure to specific antivirals, the wild-type may displace the resistant variants (Sarrazin 2007). Nevertheless, HCV quasispecies resistant to NS3-4A protease inhibitors or non-nucleoside polymerase inhibitors can be detected at low levels in some patients (approx. 1%) who have never been treated with these specific antivirals before (Gaudieri 2009). The clinical relevance of these preexisting mutants is not completely understood, although there is evidence that they may reduce the chance of achieving an SVR with DAA-based triple therapies if the patient's individual sensitivity to pegylated interferon α + ribavirin is low.

More recently, the Q80R/K variant has been described as conferring low-level resistance to simeprevir (TMC435), a macrocyclic protease-inhibitor. Interestingly, the Q80K variant can be detected in approximately 10% of HCV genotype 1-infected patients (typically in subtype 1a isolates) and a slower viral decline during simeprevir-based triple therapy was observed (Lenz 2011). Table 5.2 summarizes the resistance profile of selected NS3-4A inhibitors. Importantly, many resistance mutations can be detected *in vivo* only by clonal sequencing. For example, mutations at four positions conferring telaprevir resistance have been characterized so far (V36A/M/L, T54A, R155K/M/S/T and A156S/T), but only A156 was identified initially *in vitro* in the replicon system (Lin 2005). These mutations, alone or as double mutations, conferred low (V36A/M, T54A, R155K/T, A156S) to high (A156T/V, V36M + R155K, V36M + 156T) levels of resistance to telaprevir (Sarrazin 2007). It is thought that the resulting amino acid changes of these mutations alter the confirmation of the catalytic pocket of

the protease, which impedes binding of the protease inhibitor (Welsch 2008).

Table 5.2 – Resistance mutations to HCV NS3 protease inhibitors.

	36	54	55	80	155	156A	156B	168	170
Telaprevir* (linear)	■	■			■	■	■		
Boceprevir* (linear)	■	■	■		■	■			■
SCH900518* (linear)	■	■			■	■	■		■
BI-201335* (linear?)					■			■	
BILN-2061 ** (macrocyclic)					▒		▒	▒	
Danoprevir* (macrocyclic)					▒			▒	
MK-7009* (macrocyclic)					▒		▒	▒	
TMC435* (macrocyclic)				▒	▒		▒	▒	
BMS-650032* (macrocyclic)				▒	▒			▒	
GS-9451* (macrocyclic)					▒			▒	
ABT450* (macrocyclic)					▒			▒	
IDX320** (macrocyclic)								▒	
ACH1625** (macrocyclic)								▒	
MK-5172*** (macrocyclic)									

36: V36A/M; 54: T54S/A; 55: V55A; 80: Q80R/K; 155: R155K/T/Q; 156A: A156S; 156B: A156T/V; 168: D168A/V/T/H; 170: V170A/T

* mutations associated with resistance in patients

** mutations associated with resistance in vitro

*** no viral breakthrough during 7 days monotherapy

Q80 variants have been observed in approximately 10% of treatment-naïve patients and was associated with slower viral decline during simeprevir (TMC435) triple therapy

As shown for other NS3-4A protease inhibitors (e.g., danoprevir), the genetic barrier to telaprevir resistance differs significantly between HCV subtypes. In all clinical studies of telaprevir alone or in combination with PEG-IFN α and ribavirin, viral resistance and breakthrough occurred much more frequently in patients infected with HCV genotype 1a compared to genotype 1b. This difference was shown to result from nucleotide differences at position 155 in HCV subtype 1a (aga, encodes R) versus 1b (cga, also encodes R). The mutation most frequently associated with resistance to telaprevir is R155K; changing R to K at position 155 requires 1 nucleotide change in HCV subtype 1a, and 2 nucleotide changes in subtype 1b isolates (McCown 2009).

It will be important to define whether treatment failure due to the development of resistance has a negative impact on re-treatment with the same or other DAA treatments. Follow-up studies of telaprevir and boceprevir Phase III studies have revealed a rapid decline of resistant variants below the limit of detection (>20% of quasispecies) of population sequencing techniques (Barnard 2011, Sherman 2011). However, telaprevir- and boceprevir-resistant variants were detectable by a clonal sequencing approach several years after treatment in single patients who had been treated with telaprevir or boceprevir within smaller Phase Ib studies (Susser 2011).

NS5B polymerase inhibitors

Molecular biology

HCV replication is initiated by the formation of the replication complex, a highly structured association of viral proteins and RNA, of cellular proteins and cofactors, and of rearranged intracellular lipid membranes derived from the endoplasmic reticulum (Moradpour 2007). The key enzyme in HCV RNA replication is NS5B, an RNA-dependent RNA polymerase that catalyzes the synthesis of a complementary negative-strand RNA by using the positive-strand RNA genome as a template (Lesburg 1999) (Figure 5.4). From this newly synthesized

negative-strand RNA, numerous RNA strands of positive polarity are produced by NS5B activity that serve as templates for further replication and polyprotein translation. Because of poor fidelity leading to a high rate of errors in its RNA sequencing, numerous different isolates are generated during HCV replication in a given patient, termed HCV quasispecies. It is reasoned that due to the lack of proofreading of the NS5B polymerase together with the high replication of HCV, every possible mutation is generated each day.

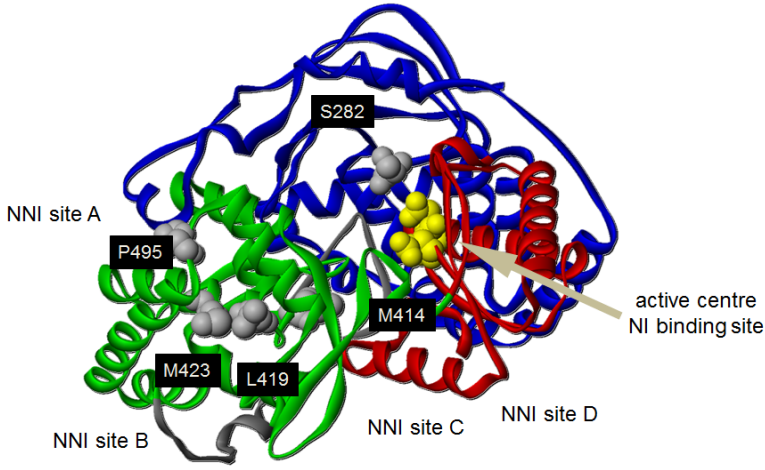

Figure 5.4 – Structure of the HCV NS5B RNA polymerase and binding sites.

NS5B RNA polymerase inhibitors can be divided into two distinct categories. Nucleoside analog inhibitors (NIs) like valopicitabine (NM283), mericitabine (R7128), R1626, GS-7977, GS-938 or IDX184 mimic the natural substrates of the polymerase and are incorporated into the growing RNA chain, thus causing direct chain termination by tackling the active site of NS5B (Koch 2006). Because the active centre of NS5B is a highly conserved region of the HCV genome, NIs are potentially

effective against different genotypes. Single amino acid substitutions in every position of the active centre may result in loss of function or in extremely impaired replicative fitness. Thus, there is a relatively high barrier to resistances to NIs.

In contrast to NIs, the heterogeneous class of non-nucleoside inhibitors (NNIs) achieves NS5B inhibition by binding to different allosteric enzyme sites, which results in conformational protein change before the elongation complex is formed (Beaulieu 2007). For allosteric NS5B inhibition, high chemical affinity is required. NS5B is structurally organized in a characteristic "right hand motif", containing finger, palm and thumb domains, and offers at least four NNI-binding sites, a benzimidazole-(thumb 1)-, thiophene-(thumb 2)-, benzothiadiazine-(palm 1)- and benzofuran-(palm 2)-binding site (Lesburg 1999) (Figure 5.4). Because of their distinct binding sites, different polymerase inhibitors can theoretically be used in combination or in sequence to manage the development of resistance. Because NNIs bind distantly to the active centre of NS5B, their application may rapidly lead to the development of resistant mutants *in vitro* and *in vivo*. Moreover, mutations at the NNI binding sites do not necessarily lead to impaired function of the enzyme. Figure 5.5 shows the structure of selected nucleoside and non-nucleoside inhibitors.

Nucleoside analogs

Mericitabine (RG7128) is the most advanced nucleoside polymerase inhibitor. Mericitabine is safe and well-tolerated, effective against all HCV genotypes, and thus far no viral resistance has been observed in clinical studies. Interim results of current Phase II clinical trials in HCV genotype 1-, 2-, 3-infected patients of R7128 in combination with pegylated interferon and ribavirin revealed superior SVR rates of mericitabine-based triple therapy compared to PEG-IFN α alone (Pockros 2011). In an all-oral regimen, administration of R7128 in combination with the protease inhibitor R7227/ITMN191 for 14 days, a synergistic antiviral activity of both drugs was observed

(Gane 2010). No viral breakthrough with selection of resistant variants has been reported.

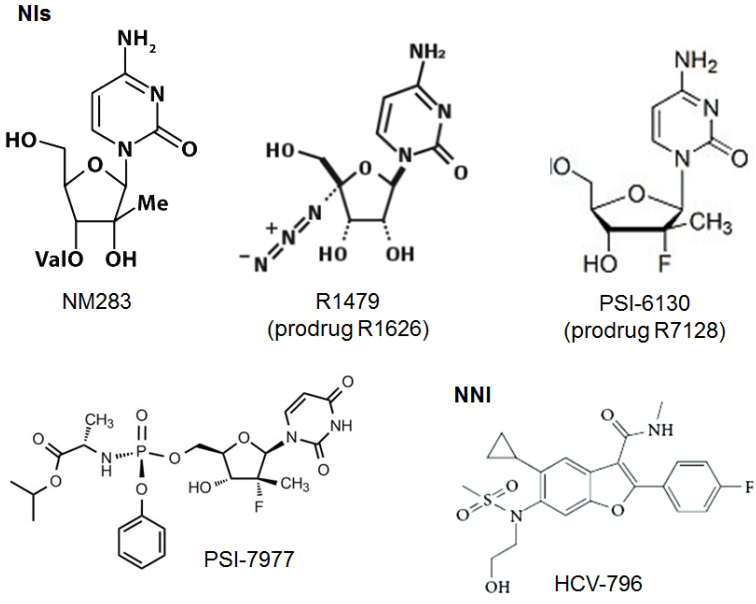

Figure 5.5 — Molecular structure of selected NS5B polymerase inhibitors.

Very promising clinical data have been published recently for GS-7977, a nucleoside analog NS5B inhibitor effective against all HCV genotypes. In HCV genotype 2- and 3-infected patients, GS-7977 (400 mg once daily) in combination with ribavirin for 12 weeks + PEG-IFN α for 4-12 weeks resulted in 100% RVR and 100% week 12 SVR rates (Gane 2011). No GS-7977-associated side effects have been reported, and no virologic breakthrough has been observed. A second study evaluated GS-7977-based triple therapy in treatment-naïve HCV genotype 1-infected patients. In this study, GS-7977 was administered for 12 weeks, together with

PEG-IFN α and ribavirin for 24 or 48 weeks in total, according to whether HCV RNA was below the limit of detection at treatment weeks 4 and 12 or not, respectively (Lawitz 2011). Most patients were eligible for the shortened treatment duration of 24 weeks, and SVR was achieved in approximately 90% of all patients.

Other nucleoside analogs (e.g., GS-938 (currently on hold due to increased liver enzymes) and IDX184) are at earlier stages of clinical development (Sarrazin 2010).

Overall, the newer nucleoside analogs (GS-7977, GS-938) also demonstrate high antiviral activities that, together with their high genetic barrier to resistance, suggest that they are optimal candidates for all-oral combination therapies (see below).

Non-nucleoside analogs

At least 4 different allosteric binding sites have been identified for inhibition of the NS5B polymerase by non-nucleoside inhibitors. Currently, numerous non-nucleoside inhibitors are in Phase I and II clinical evaluation (Table 5.1) (Ali 2008, Cooper 2007, Erhardt 2009, Kneteman 2009). In general, these non-nucleoside analogs display a low to medium antiviral activity and a low genetic barrier to resistance, evidenced by frequent viral breakthrough in monotherapy studies and selection of resistance mutations at variable sites of the enzyme. In line with these experiences in Phase I studies, a Phase II triple therapy study with filibuvir plus pegylated interferon and ribavirin showed high relapse and relative low SVR rates (Jacobson 2010). In contrast to nucleoside analogs, non-nucleoside analogs in general do not display antiviral activity against different HCV genotypes (Sarrazin 2010). Due to their low antiviral efficacy and low genetic barrier to resistance, non-nucleoside analogs will probably not be developed as part of triple therapy but rather as components of quadruple or all-oral regimens (see below).

NS5A inhibitors

The HCV NS5A protein seems to play a manifold role in HCV replication, assembly and release (Moradpour 2007). It was

shown that NS5A is involved in the early formation of the replication complex by interacting with intracellular lipid membranes, and it initiates viral assembly at the surface of lipid droplets together with the HCV core (Shi 2002). NS5A may also serve as a channel that helps to protect and direct viral RNA within the membranes of the replication complex (Tellinghuisen 2005). Moreover, it has been demonstrated that NS5A is able to interact with NS5B, which results in an enhanced activity of the HCV RNA polymerase. Besides its regulatory impact on HCV replication, NS5A has been shown to modulate host cell signaling pathways, which has been associated with interferon resistance (Wohnsland 2007). Furthermore, mutations within the NS5A protein have been clinically associated with resistance / sensitivity to IFN-based antiviral therapy (Wohnsland 2007).

BMS-790052 was the first NS5A inhibitor to be clinically evaluated. Even low doses of BMS-790052 display high antiviral efficacy against all HCV genotypes *in vitro*. Monotherapy with BMS-790052 led to a sharp initial decline of HCV RNA concentrations, though its genetic barrier to resistance is relatively low (Gao 2010). In an interim analysis of a Phase IIb clinical trial in treatment-naïve HCV genotype 1 and 4 patients, treatment with 20 or 60 mg BMS-790052 once daily in combination with PEG-IFN α and ribavirin for 24 or 28 weeks, 54% of all patients achieved an extended RVR, compared to 13% in the control group (Hezode 2011). SVR rates of this study are awaited.

During monotherapy, rapid selection of variants resistant to BMS-790052 occurred (Nettles 2011). The most common resistance mutations in HCV genotype 1a patients were observed at residues M28, Q30, L31, and Y93 of NS5A. In HCV genotype 1b patients, resistance mutations were observed less frequently, predominantly at positions L31 and Y93. These resistance mutations increased the EC50 to BMS-790052 moderately to strongly (Fridell 2011). However, no cross-resistance between BMS-790052 and other DAA agents has been reported. Collectively, BMS-790052 is a highly promising agent for both

triple therapy as well as all-DAA combination therapy approaches.

Other NS5A inhibitors (e.g., BMS-824393, PPI-461, GS-5885) are in early clinical development.

Combination therapies of specific antivirals

It is a fundamental question whether an SVR can be achieved with combination therapies of different DAA compounds without PEG-IFN α and ribavirin. A first clinical trial (INFORM-1) evaluated the combination of a polymerase inhibitor (Mericitabine (R7128)) and a NS3 inhibitor (R7227/ITMN191). In this proof of principle study, patients were treated with both compounds for up to 2 weeks. HCV RNA concentrations decreased up to 5.2 $\log_{10}$ IU/ml, viral breakthrough was observed in only one patient (but no resistant HCV variants were identified), and HCV RNA was undetectable at the end of dosing in up to 63% of treatment-naïve patients (Gane 2010). Several trials are ongoing to further define the potential of all-oral regimens, including NS3 protease inhibitors, nucleoside and non-nucleoside NS5B inhibitors, NS5A inhibitors, and ribavirin. Recent interim analyses indicate that most patients treated with only two DAA agents experience viral breakthrough, which can be significantly reduced by the addition of ribavirin without PEG-IFN α (Zeuzem 2011).

Host factors as targets for treatment

Cyclophilin B inhibitors

HCV depends on various host factors throughout its life cycle. Cyclophilin B is expressed in many human tissues and provides a cis-trans isomerase activity, which supports the folding and function of many proteins. Cyclophilin B enhances HCV replication by incompletely understood mechanisms, like the modulation of NS5B activity. Debio-025 (alisporivir) is an orally bioavailable cyclophilin B inhibitor exerting an antiviral impact on both HCV and HIV replication. In clinical trials in HIV/ HCV-

coinfected patients, treatment with 1200 mg Debio-025 twice daily for two weeks led to a mean maximal log_{10} reduction of HCV RNA of 3.6 and of HIV DNA of 1.0 (Flisiak 2008). Debio-025 was well-tolerated and no viral breakthrough occurred during the 14 days of treatment.

Combination therapy of Debio-025 200 mg, 600 mg or 1000 mg and PEG-IFN α-2a was evaluated in a double-blind placebo-controlled Phase II trial in treatment-naïve patients monoinfected with HCV genotypes 1, 2, 3 or 4. Treatment was administered for 29 days. Mean log_{10} reductions in HCV RNA at day 29 were 4.75 (1000 mg), 4.61 (600 mg) and 1.8 (200 mg) in the combination therapy groups compared to 2.49 (PEG-IFN α-2a alone) and 2.2 (1000 mg Debio-025 alone) in the monotherapy groups. No differences in antiviral activity were observed between individuals infected with the different genotypes. Debio-025 was safe and well-tolerated but led to a reversible bilirubin increase in some patients treated with 1000 mg Debio-025 daily (Flisiak 2009). A high genetic barrier to resistance of Debio-025 and a broad HCV genotypic activity highlight the potential of drugs targeting host proteins.

In a Phase II clinical trial in treatment-naïve HCV genotype 1 patients, combination therapy with Debio-025, PEG-IFN α-2a and ribavirin for 24-48 weeks resulted in SVR rates of 69-76% compared to 55% in the control group (Flisiak 2011).

Silibinin

Silymarin, an extract of milk thistle (*Silybum marianum*) with antioxidant activity, has been used to treat chronic hepatitis C and other liver diseases. Silibinin is one of the six major flavonolignans in silymarin. Surprisingly, recent reports demonstrated that silibinin inhibits HCV at various steps of its life cycle (Ahmed-Belkacem 2010, Wagoner 2010). In addition, intravenous silibinin in non-responders to prior IFN-based antiviral therapy led to a decline in HCV RNA between 0.55 and 3.02 log_{10} IU/ml at 7 days and a further decrease after an additional 7 days in combination with PEG-IFN α-2a/RBV in the

range of 1.63 and 4.85 $\log_{10}$ IU/ml (Ferenci 2008). Ongoing studies will clarify the role of silibinin in the treatment of chronic hepatitis C, including HCV liver graft reinfection.

Miravirsen

MicroRNA-122 (miRNA-122) is a liver-specific microRNA that has been shown to be a critical host factor for HCV (Landford 2010). MiRNA-122 binds to the 5´NTR region of the HCV genome, which appears to be vital in the HCV replication process. Miravirsen is a modified antisense oligonucleotide that targets miRNA-122 and thereby prevents binding of miRNA-122 to the HCV genome. In a Phase IIa proof-of-principle study, weekly subcutaneous injections of miravirsen led to a reduction of HCV RNA serum concentration of up to 2.7 $\log_{10}$ IU/mL, indicating that an antisense oligonucleotide-based approach of miRNA-122 inhibition could be a promising modality for antiviral therapy (Janssen 2010). No relevant side effects were seen in this study.

Newer combination therapies

The approval of the HCV protease inhibitors telaprevir and boceprevir in 2011 constitutes a milestone in the treatment of chronic HCV genotype 1 infection. Nevertheless, telaprevir- or boceprevir-based triple therapy has certain limitations. In particular, treatment success still depends on the interferon-sensitivity of individual patients because a slow decline of HCV viral load during triple therapy is associated with a high risk of antiviral resistance development. Consequently, viral breakthrough of drug resistant variants was observed in a significant number of patients with partial or null response to previous treatment with PEG-IFN α and ribavirin, in patients with limited decline of HCV viral load during lead-in treatment with PEG-IFN α and ribavirin alone, or in difficult-to-cure populations like blacks or patients with advanced liver fibrosis. In addition, triple therapy is not an option for patients with

contraindications to PEG-IFN α or ribavirin, such as patients with decompensated liver cirrhosis or liver transplant failure.

To overcome these limitations, numerous trials have been initiated to investigate the potential of combination therapies with different DAA agents alone (Table 5.3). As is well established in the treatment of HIV infection, combining DAA agents with different antiviral resistance profiles should result in a substantially decreased risk of viral breakthrough of resistant variants. Nucleoside analog NS5B inhibitors plus drugs targeting host factors such as the cyclophilin inhibitor alisporivir display a high genetic barrier to resistance development and may therefore be key agents for effective DAA combination therapies (Sarrazin 2010). In contrast, NS3-4A and NS5A inhibitors display a low genetic barrier to resistance development, but in view of their high antiviral efficacy they appear to be promising combination partners for nucleoside analogs or cyclophilin inhibitors. Due to their low antiviral efficacy and low genetic barrier to resistance development, the role of non-nucleoside analog NS5B inhibitors is currently less clear. A potential advantage of non-nucleoside analogs is their binding to multiple target sites that may allow simultaneous treatment with several non-nucleoside analogs.

Currently, DAA combination treatment regimens can be classified according to the usage of PEG-IFN α into quadruple therapy regimens and all-oral therapy regimens. Quadruple therapy approaches are based on therapy of PEG-IFN α and ribavirin plus combination of two DAA agents from different classes. In contrast, all-oral treatment comprises interferon-free regimens including combinations of various DAA compounds with or without ribavirin.

Quadruple therapy

Preliminary SVR data of a small but highly informative trial serves as a proof-of-concept for the potential of quadruple therapy approach for patients with previous null response to PEG-IFN α + ribavirin (Lok 2011). In this Phase II study, 11 HCV

genotype 1 patients with prior null response were treated with a combination of the NS5A inhibitor BMS-790052 and the protease inhibitor BMS-650032 together with PEG-IFN α and ribavirin for 24 weeks. Quadruple therapy resulted in 100% SVR 12 weeks after treatment completion in both HCV genotype 1a- and 1b-infected patients. Even though the number of patients included in this trial was very limited, this high SVR rate after quadruple therapy seems impressive compared to SVR rates of ~30% that were achieved with telaprevir-based triple therapy in prior null responders (Zeuzem 2011).

A Phase II clinical trial assessed quadruple therapy with the non-nucleoside NS5B inhibitor tegobuvir in combination with the NS3-4A inhibitor GS-9256 + PEG-IFN α and ribavirin for 28 days in treatment-naïve HCV genotype 1 patients (Zeuzem 2011). The primary endpoint of this study was rapid virologic response (RVR), which was achieved in 100% of patients. After 28 days of quadruple therapy, treatment with PEG-IFN α and ribavirin was continued, which led to complete early virologic reponse (cEVR) in 94% of patients (Zeuzem 2011).

Another Phase II clinical trial investigated a response-guided approach during quadruple therapy containing the non-nucleoside NS5B inhibitor VX-222 (100 mg or 400 mg) in combination with the NS3-4A inhibitor telaprevir + PEG-IFN α and ribavirin in treatment-naïve HCV genotype 1 patients (Nelson 2011). Quadruple treatment was administered for 12 weeks. All treatment was stopped after 12 weeks in patients who were HCV RNA-negative at treatment weeks 2 and 8. Patients in whom HCV RNA was detectable at treatment week 2 or 8 received an additional 12 weeks of PEG-IFN α and ribavirin alone. Some 50% of patients met the criteria for the 12-week treatment duration. Of those, 82-93% achieved an SVR 12 weeks after treatment completion. In patients who were treated with an additional 12 weeks of PEG-IFN α and ribavirin, the end-of-treatment response was 100%.

Collectively, the quadruple therapy approach appears to be highly promising in patients with limited sensitivity to interferon α, even in patients with HCV subtype 1a.

All-oral therapy

A first interferon-free clinical trial (the INFORM-1 study) evaluated the combination of a polymerase inhibitor (R7128) and an NS3 inhibitor (R7227/ITMN191). In this proof of principle study, patients were treated with both compounds for up to 2 weeks (Gane 2010). HCV RNA concentrations decreased by up to 5.2 $\log_{10}$ IU/ml, and viral breakthrough was observed in only one patient (although no resistant HCV variants were identified), and HCV RNA was undetectable at the end of dosing in up to 63% of treatment-naïve patients. However, the fundamental question of whether an SVR can be achieved with combination therapies of different DAA compounds without PEG-IFN α and ribavirin was not answered by this trial.

SVR data are available for a Phase II clinical trial investigating therapy with the NS5A inhibitor BMS-790052 in combination with the NS3-4A protease inhibitor BMS-650032 for 24 weeks in 10 HCV genotype 1 patients with a previous null response to PEG-IFN α and ribavirin (Lok 2011). 36% of patients achieved an SVR 24 weeks after treatment completion. All patients with viral breakthrough were infected with HCV genotype 1a, and in all of them HCV variants with resistance mutations against both agents were detected. Although data of longer follow-up periods are needed, this trial constitutes a proof-of-principle that SVR can be achieved via all-oral regimens, even in patients infected with HCV subtype 1b. This was confirmed with a 100% SVR rate in a small study evaluating the same agents (BMS-790052 and BMS-650032) in Japanese HCV genotype 1b previous null responders (Chayama 2011).

Another trial has investigated 12 weeks of GS-7977 monotherapy (400 mg once daily) in HCV genotype 2- and 3-infected patients (n=10). 100% of patients achieved an RVR and

EOTR, which translated into an SVR in 60% of patients (Gane 2011).

All-oral therapy with ribavirin

Two trials evaluated all-oral DAA combination therapies with ribavirin. In one of them, combination therapy of the NS3-4A inhibitor BI201335, the non-nucleoside NS5B inhibitor BI207127 (400 or 600 mg TID) and ribavirin for 4 weeks was assessed (Zeuzem 2011). Virologic response rates in patients treated with 600 mg TID of BI-207127 were 82%, 100% and 100% at treatment days 15, 22, and 29, respectively (Zeuzem 2011). In patients who received the lower dose of BI-207127, virologic response rates were significantly lower, and in these patients lower virologic response rates were observed for patients infected with HCV subtype 1a compared to subtype 1b.

Another trial compared tegobuvir (a non-nucleoside NS5B inhibitor) + GS-9256 (a NS3-4A inhibitor) with or without ribavirin in treatment-naïve HCV genotype 1 patients (Zeuzem 2011). Importantly, tegobuvir + GS-9256 + ribavirin led to a higher HCV RNA decline after 28 days of treatment compared to tegobuvir + GS-9256 alone (-5.1 $\log_{10}$ vs. -4.1 $\log_{10}$, respectively), indicating that ribavirin might be an important component of interferon-free DAA combination therapies. SVR data of these and additional combination therapy regimens are expected in the near future.

Additional trials investigated all-oral combination regimens with ribavirin in HCV genotype 2 and 3 patients. 12 weeks of GS-7977 plus ribavirin resulted in 100% RVR, EOTR, and SVR rates in a small number of treatment-naïve patients (n=10) (Gane 2011). However, in HCV genotype 1 patients, this treatment regimen may be less efficient since 6 out of 10 HCV gentoype 1 patients with prior null-reponse expierenced a viral relapse after the end of a 12-week treatment with GS-7977 plus ribavirin (Gilead Press Release 2012).

In another study evaluating the cyclophilin A inhibitor alisporivir in combination with ribavirin, only approximately

50% of HCV genotype 2 and 3 patients became HCV RNA-negative at treatment week 6 (Pawlotsky 2011). Nevertheless, these data highlight the impressive potential of all-oral regimens, when agents with little risk of antiviral resistance development such as nucleoside analog NS5B inhibitors are used in combination with ribavirin.

Table 5.3. Selected trials evaluating DAA combination therapies.

DAAs combined	Additional medication	Phase
BMS-650032 (NS3-4A inhibitor) + BMS-790052 (N5A inhibitor)	+ / - PEG-IFN α and ribavirin	II
BI-201335 (NS3-4A inhibitor) + BI-207127 (non-nuc. NS5B inhibitor)	+ ribavirin + / - PEG-IFN α	II
GS-9190 (non-nuc. NS5B inhibitor) + GS-92568 (NS3-4A inhibitor)	+ / - ribavirin + / - PEG-IFN α	II
Danoprevir (NS3-4A inhibitor) + RG-7128 (nuc. NS5B inhibitor)	followed by PEG-IFN α and ribavirin	II
Telaprevir (NS3-4A inhibitor) + VX-222 (non-nuc. NS5B inhibitor)	+ / - ribavirin + / - PEG-IFN α	II
GS-938 (purine nuc. NS5B inhibitor) + GS-7977 (pyrimidine nuc. NS5B inhibitor)	-	II

Novel interferons

Over the last years, attempts have been made to reduce side effects and treatment discomfort of PEG-IFN α. However, interferons with longer half-life and sustained plasma concentrations (e.g., albinterferon, a fusion protein of IFN α-2b with human albumin) have so far shown no overall benefit with respect to SVR rates (Zeuzem 2010). Still promising is the development of pegylated interferon lambda 1 (PEG-IFN lambda 1). Like other type 3 interferons, IFN lambda 1, which is also called interleukin-29 (IL-29), binds to a different receptor than IFN α, but downstream signaling pathways of IFN lambda and IFN α are largely comparable. The IFN lambda receptor is predominantly expressed in hepatocytes. Thus, interferon-

related side effects may be less frequent during PEG-IFN lambda treatment. A Phase I clinical trial evaluating pegylated interferon lambda with or without ribavirin was completed (Muir 2010) and the interferon lambda was well-tolerated with the majority of patients achieving a greater than 2 $\log_{10}$ decline of HCV RNA by 4 weeks. According to an interim analysis of a subsequent Phase II clinical trial, PEG-IFN lambda (240 ug, 180 ug, or 120 ug once weekly) was compared to PEG-IFN α-2a. PEG-IFN lambda at doses of 240 or 180 ug, and resulted in approximately 10% higher RVR and 20% higher cEVR rates, and a lower frequency of flu-like symptoms, although with more frequent aminotransferase and bilirubin elevations than PEG-IFN α-2a (Zeuzem 2011).

Conclusions

Telaprevir- and boceprevir-based triple therapy of treatment-naïve and treatment-experienced HCV genotype 1 patients results in substantially increased SVR rates compared to PEG-INF α and ribavirin alone. The approval of these agents represents a major breakthrough in the treatment of chronic hepatitis C. However, successful use of these drugs will require a precise classification of response patterns to previous treatment, careful on-treatment monitoring of HCV viral load and emergence of antiviral resistance as well as of additional side effects and numerous possible drug-drug interactions. Next-generation NS3-4A protease inhibitors and NS5A inhibitors may have even more favorable properties than telaprevir and boceprevir in terms of HCV genotype coverage, safety profiles, less pronounced drug-drug interactions, or possible once-daily administration. However, the current triple therapy approach has several limitations. First of all, efficacy of triple therapy was limited in prior null responders to PEG-IFN α and ribavirin, and triple therapy cannot be administered to patients with contraindications to PEG-IFN α or ribavirin. Recent data indicate that the development of DAA combination therapies in all-oral

or quadruple treatment regimens will likely be a very potent option for these patients. In such DAA combination regimens, the inclusion of drugs with a high genetic barrier to resistance such as nucleoside NS5B inhibitors or drugs such as alisporivir that target host factors may be important.

6. Adverse Events and Drug Interactions

Martin Schaefer and Stefan Mauss

Good adherence is a key factor for success in the treatment of hepatitis C. However, almost all patients on treatment with interferon plus ribavirin will experience side effects that can threaten good adherence. Therefore, proactive management of adverse events is crucial to avoid suboptimal therapy (missed doses, etc) and treatment discontinuation. The most common clinical adverse events in patients on treatment with pegylated interferon plus ribavirin are flu-like symptoms, myalgia, sleep disturbances, asthenia, gastrointestinal disorders and depressive mood changes.

For most adverse events, clinical trials looking at dose moderation have not been done and because of this, recommendations for management are in great part based on clinical experience.

Systemic Symptoms

Flu-like symptoms, fever, arthralgia and myalgia will usually diminish spontaneously during the first weeks of treatment.
Gastrointestinal disorders. Nausea and loss of appetite, dry mouth.

Weight loss in interferon-based studies is around 6-10% at 48 weeks (Seyam 2005) due to loss of appetite and reduction in calorie intake.
Asthenia and fatigue are frequent complaints that usually increase slowly in intensity over the first couple weeks of therapy. Asthenia is also reported by patients without marked anemia. In these patients hypothyroidism has to be excluded. Treatment in patients without an underlying complication such as anemia, depression or hypothyroidism is difficult. For chronic fatigue, currently available data does not point to specific treatment recommendations.
Cough is frequently reported and is most probably due to oedema of the mucosa of the respiratory system. Advanced, not well-controlled asthma bronchiale may be a contraindication for hepatitis C therapy. Dyspnea is another frequent complaint.
Hypothyroidism and hyperthyroidism are seen, possibly due to an interferon-induced thyroiditis or the induction of thyroid antibodies. Premature termination of interferon-based therapy is usually not necessary.

Psychiatric Adverse Events

The most common IFN α-induced psychiatric adverse events are outlined in Tables 6.1 and 6.2. Most hepatology trials are only monitored for "major depression" without using depression scales, leading to an underreporting of mild to moderate depressive episodes.

Treatment adherence should be assessed by monitoring serum levels before patients are switched to a different antidepressant.

Although history of major depression or suicide attempts is considered a contraindication for interferon-based therapy, treatment of patients with pre-existing psychiatric disorders can be initiated in close collaboration with an experienced psychiatrist in a well-controlled setting (Schaefer 2004, Schaefer 2007b).

Table 6.1 – Incidence of the most reported IFN α-induced psychiatric side effects.

Psychiatric side effects	Incidence
Fatigue	50-80%
Sleep disturbances	45-65%
Irritability	60-85%
Cognitive disturbances with impairment of concentration and memory	45-60%
Depressive episodes	20-60%
- Mild	30-60%
- Moderate	20-30%
- Severe	5-10%
Delirium, psychosis	1-6%
Suicidal syndrome	<1%

Table 6.2 – Frequency of psychiatric adverse events with IFN α + RBV.

Incidence	Effects
>50%	Sleep disorders, chronic fatigue, irritability or cognitive disturbances (Schaefer 2007a, Schaefer 2002, Dieperink 2000, Renault 1987)
30-45%	Anxiety, esp. during first two months
30-60%	Mild depression – reduced self-esteem, anhedonia, loss of interest, rumination, diminished libido, spontaneous crying
20-30%	Moderate to severe depressive episodes (Bonnaccorso 2002, Dieperink 2000, Renault 1987, Schaefer 2002, Malaguarnera 2002)
5-6%	Suicidal ideation
Individual Cases	Suicide attempts (Janssen 1994)
Sporadic	Mania

Treatment with antidepressants can be started at a relatively low dose, increasing depending on the effect and tolerability.

Current data supports the view that all patients with pre-existing depressive symptoms should receive a prophylactic treatment with antidepressants (Musselman 2001, Capuron 2002, Krauss 2005, Raison 2007). Evidence from larger prospective

controlled studies is still needed in order to define if prophylactic antidepressants are useful across the board for all patients.

As sleeping disorders can be a symptom of depression, it is also important to identify and assess existing depressive symptoms when considering the use of sleeping aids.

Hematologic and immunologic effects

In general the incidence of serious infections is low (<5%) in patients on interferon-based therapy. Despite some reassuring clinical data, G-CSF is not often used to correct neutropenia because it has not been studied for this purpose and its use is off-label.

For mild to moderate thrombocytopenia in advanced liver fibrosis, eltrombopag may be used cautiously (Afdhal 2011).

Skin disorders

Skin disorders such as lichen ruber planus, necrotising vasculitis or porphyrea cutanea tarda are associated with hepatitis C infection. Local skin reactions to the injection of pegylated interferon are common. Repeated injections at the same site may cause ulcers and should be avoided. Hair loss is frequent, usually appearing after the first months of therapy and continuing for some weeks after the cessation of therapy but is usually fully reversible, although the structure of the hair may be different after therapy. Alopecia is very rare. Many other side effects are outlined in Tables 6.3 and 6.4.

Table 6.3 – What to expect and what to do (I).

Symptom	When/why/ Duration (D)	Treatments	Caution
Flu-like symptoms	Immediately post-IFN injection / D: 3 days	<2 g paracetamol, NSAIDs	Low platelets, liver toxicity
Loss of appetite		Pre-RBV: metoclopramide, domperidone	
Dry mouth	With RBV/ D: May continue post-therapy		
Weight loss	During treatment/ D: On treatment	Reversible on discontinuation	6-10% loss over 48 wks
Asthenia, fatigue	First few weeks of treatment/ D: Increases over time	Erythropoietin, reduce RBV dosage, red blood cell transfusion, antidepressants, tryptophan, odanestron	

The main adverse events seen with telaprevir are pruritus and rash, with the first occurring in the majority of patients. Pruritus can be orally treated with antihistamines, e.g., cetirizine. The rash is usually mild to moderate and serious skin reactions seem to be rare. Discontinuation is rarely necessary. Intermittent use of corticosteroid-based ointments together with rehydrating and/or urea containing creams are the treatments of choice for rash. With psoriasis a consultation of an experienced dermatologist is advisable. Anaemia is seen and may require dose adjustment of ribavirin or in some cases the use of erythropoietin or red blood cell transfusion. Nausea and diarrhoea are seen frequently in patients on telaprevir (Hézode 2009, McHutchison 2009, McHutchison 2010, Marcellin 2011).

For boceprevir, anemia is the most important adverse event requiring dose adjustment of ribavirin or in some cases the use of erythropoietin or red blood cell transfusion in a considerable number of patients. Nausea and diarrhea are seen frequently in patients on boceprevir. Treatment of skin adverse events is similar to that for telaprevir-associated skin toxicity (Anonymous 2010).

Table 6.4 – What to expect and what to do (II).

Symptom	When/why/ Duration (D)	Treatments	Caution
Hypothyroidism	Can occur at any time	L-thyroxin replacement therapy	
Cough	Oedema of resp. mucosa / D: On treatment	Local therapy of fluticasone or budesonide	
Hypothyroidism	IFN / 3-10% reversible on discontinuation	Substitution of thyroid hormone	
Hyperthyroidism	1-3%	B-blockers, carbimazole	
Psychiatric effects	On IFN, pre-existing[1] or not[6]	SSRIs (citalopram[2], paroxetin) Mirtazapine[3] Nortriptiline[4] Tricyclics (doxepine)	Tricyclics are 2nd choice – interactions and delirium, heart, liver complications
Agitation/ aggression		Antipsychotics (risperidone, olanzapine)	Monitor with psychiatrist
Severe sleep disturbances, irritability, depression		Benzodiazapines[5], zolpidem, trimipramine	[5]Can induce addiction
Hemolytic anemia	RBV	RBV dose reduction RBC transfusion Erythropoetin[7]	
Thrombocytopenia	In advanced liver fibrosis	IFN dose reduction Eltrombopag[8]	
Dry skin, itching, eczema, exacerbation of psoriasis	HCV, IFN, RBV	Urea ointments, steroids	Involve dermatologist May continue post-treatment
Hypersensitivity	PEG-IFN		Anecdotal

1. Schaefer 2005. 2. Krauss 2008. 3. Krauss 2001. 4. Valentine 1995. 5. Schaefer & Mauss 2008. 6. Schaefer 2007b; Schaefer 2003; Pariante 2002. 7. Afdahl 2004; Pockros 2004; Shiffman 2007. 8. McHutchinson 2007.

Telaprevir and boceprevir

Triple therapy that includes one of the newer HCV protease inhibitors is standard of care for most genotype 1 patients. This

treatment provides new challenges for adherence and management of adverse events. While all adverse events caused by interferon and ribavirin remain, some may be accentuated or new adverse events may occur.

Frequent adverse events seen with telaprevir are itching and rash, with the first occurring in the majority of patients. Itching can be orally treated with antihistamines, e.g., cetirizine, but efficacy seems limited. Rash is usually mild to moderate while serious skin reactions seem to be rare. Use of corticosteroid-based ointments, e.g., betamethasone 0.1% together with rehydrating and/or urea-containing creams are the treatments of choice for rash. For a serious case of psoriasis a consultation with an experienced dermatologist is advisable. Discontinuation is rarely necessary. Anal symptoms ranging from discomfort to pain and bleeding are also common. Depending on the severity, local therapy with a zinc paste or corticosteroid ointments are used.

A more frequent and more pronounced anemia than what is seen with interferon plus ribavirin may require dose adjustment of ribavirin or red blood cell transfusion. The use of erythropoietin for mitigation of anemia is not approved, but can be tried where reimbursement is possible.

Nausea and diarrhea are frequently seen in patients and may require symptomatic therapy (Hézode 2009, McHutchison 2009, McHutchison 2010, Marcellin 2011).

With boceprevir, anemia is the most important adverse event requiring dose adjustment of ribavirin or red blood cell transfusion in a considerable number of patients. Dysgeusia is another frequent complaint that resolves upon discontinuation (Bacon 2011, Poordad 2011).

Boceprevir or telaprevir doses should never be reduced in case of toxicities, but rather discontinued or kept at the standard dose. Reducing the dosage of the protease inhibitors will result in treatment failure due to lower drug exposure.

In addition, boceprevir and telaprevir are simultaneous inducers and inhibitors of multiple enzymes of the cytochrome

P450 system. For this reason, drug-drug interactions are not easy to predict and involve frequently used drugs such as sedatives, antidepressants, antibiotics, immunosuppressants, oral corticosteroids, statins and calcium channel blockers. As this is an evolving area, for updated information, the website **www.hep-druginteractions.org** should be checked regularly.

Conclusion

In summary, the toxicity of interferon-based therapy in combination with ribavirin is considerable and requires the medical team to be fully knowledgeable for active management with the patient.

The first generation of HCV protease (and polymerase) inhibitors is combined with interferon and ribavirin as triple therapy, at the cost of increased toxicity. In this setting, early assessment and robust management of adverse events may help improve the quality of life of patients, prevent premature treatment discontinuations and improve the efficacy of the new hepatitis C therapy.

7. Extrahepatic Manifestations

Karl-Philipp Puchner, Albrecht Böhlig and Thomas Berg

Patients with chronic hepatitis C virus (HCV) infection are at risk of a great number of extrahepatic manifestations (EHMs) (Table 7.1) – up to 40-76% of patients infected with HCV develop at least one EHM during the course of the disease (Cacoub 2000, Cacoub 1999). EHMs are often the first and only clinical sign of chronic hepatitis C infection. Evidence of HCV infection should always be sought out in cases of non-specific chronic fatigue and/or rheumatic, hematological, endocrine or dermatological disorders. The pathogenesis of EHM is not fully understood, although most studies suggest that the presence of mixed cryoglobulinemia (MC), particular lymphotropism of the virus, molecular mimicry and non-cryoglobulinemic autoimmune phenomena constitute the major pathogenic factors (Ferri 2007). The pathogenesis and epidemiology of many EHMs require further investigation (Figure 7.1). Our aim is to give an insight into the epidemiology, pathogenesis, clinical relevance and therapeutic management of HCV-associated EHM (Zignego 2007a).

Table 7.1 – HCV-related extrahepatic manifestations.

Organ / System	Manifestation
Endocrine disorders	Autoimmune thyroidopathies, esp. Hashimoto thyroiditis
	Insulin resistance/diabetes mellitus*
	GH insufficiency
Rheumatic disorders	Mixed cryoglobulinemia*
	Cryglobulinemic vasculitis*
	Peripheral neuropathy*
	Membranoproliferative glomerulonephritis (GN)*
	Membranous GN*
	Rheumatoid arthralgias/oligopolyarthritis
	Rheumatoid factor positivity*
	Sicca syndrome
Hemotologic disorders	Lymphoproliferative disorders/Non-Hodgkin Lymphomas*
	Immune thrombocytopenic purpura (ITP)
	Monoclonal gammopathies*
	Autoimmune hemolytic anemia
Dermatologic disorders	Palpable purpura
	Porphyria cutanea tarda (PCT)
	Lichen planus
	Pruritus
Miscellaneous	Chronic fatigue*, subclinical cognitive impairment, psychomotoric deceleration, symptoms of depression*
	Myopathy
	Cardiomyopathy/Myocarditis
	Idiopathic pulmonal fibrosis

* Associations with strong epidemiological prevalence and/or clear pathogenetic mechanisms

Lymphoproliferative Disorders

Cryoglobulinemia refers to the presence of abnormal immunoglobulins in the serum. Cryoglobulins (CGs) are classified into three types. Type II CG, consisting of monoclonal and/or polyclonal immunoglobulins, are prevalent in patients with chronic HCV infection, while type I CGs, consisting exclusively of monoclonal components, are mostly found in patients with lymphoproliferative disorders. Type II or type III mixed

cryoglobulinemia (MC) are found in 19%-50% of patients but leads to clinical manifestations in only 30% of them (Lunel 1994, Wong 1996). Patients with symptomatic mixed cryoglobulinaemia exhibit higher cryoglobulin concentrations (Weiner 1998) and lower concentrations of complement factors C3 and C4. Factors that seem to favour the development of MC are female sex, age, alcohol intake (>50g/d), advanced liver fibrosis and steatosis (Lunel 1994, Wong 1996, Saadoun 2006). The diagnosis of MC syndrome is based on serologic, pathologic and clinical criteria (Table 7.2).

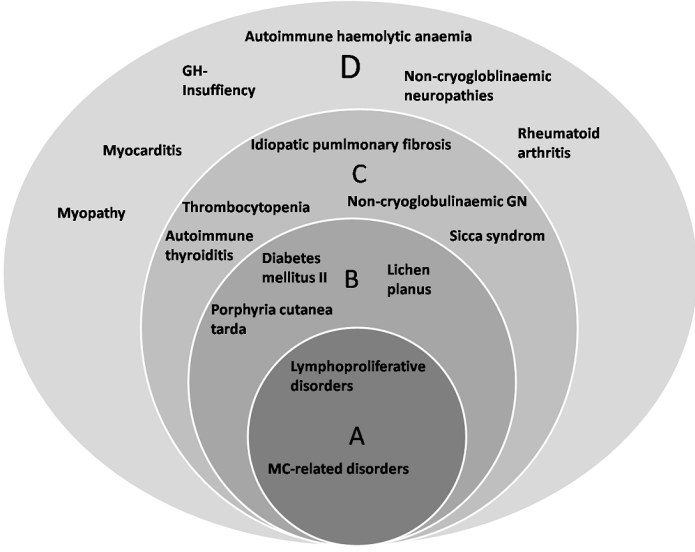

Figure 7.1 – Schematic representation of EHM categories (modified after Zignego 2007a). A) Associations with strong epidemiological evidence and clear pathogenetic mechanisms; B) Associations with high prevalence, but unclear pathogenetic mechanisms; C) Associations for which high prevalence in HCV could be due to HCV infection and/or confounding factors; D) Anecdotal observations.

Table 7.2 – Diagnostic criteria of cryoglobulinaemic syndrome.

Serologic	Histologic	Clinical
C4 reduction	Leukocytoclastic vasculitis	Purpura
Positive rheumatoid factor (RF)	Infiltrates of monoclonal B cells	Fatigue
CGs type II or III		Arthralgia
HCV antibodies		Membranoproliferative GN
		Peripheral neuropathy

In the presence of mixed CG, low C4 counts, leucocytoclastic vasculitis and purpura, a definite symptomatic MC can be diagnosed. Rheumatoid factor (RF) determination constitutes a reliable surrogate parameter for detection of CG.

Clinical features of mixed cryoglobulinemia. HCV-related MC proceeds mostly asymptomatically and has no significant influence on the course of chronic liver inflammation. On the other hand, symptomatic mixed cryoglobulinemia is associated with higher mortality (Ferri 2004). Clinical manifestations of symptomatic mixed cryoglobulinemia are systemic vasculitis, renal impairment, peripheral neuropathy and cirrhosis.

Malignant Lymphoproliferative Disorders/NHL

The most prevalent HCV-associated lymphoproliferative disorders according to the REAL/WHO classification are: follicular lymphoma, B cell chronic lymphocytic leukemia/small lymphocyte lymphoma, diffuse large B cell lymphoma and marginal zone lymphoma, including the mucosa-associated lymphoid tissue lymphoma. Marginal zone lymphoma appears to be the most frequently encountered low grade B cell lymphoma in HCV patients. 8%-10% of mixed cryoglobulinemia type II evolve into B cell NHL after long-lasting infection. However, a remarkably high prevalence of B cell NHL was also found in HCV patients without mixed cryoglobulinemia (Silvestri 1997). Genetic predisposition and other factors seem to have a major impact on the development of LPDs in HCV-positive patients (Matsuo 2004).

Etiology and pathogenesis of LPDs. In the development of LPDs direct and indirect pathogenic HCV-associated factors are seen. Sustained B cell activation and proliferation in chronic HCV infection is an indirect pathogenic mechanism. Direct pathogenic mechanisms are based on lymphotropic properties of HCV, hence on the invasion of HCV into the B cells. A direct involvement of HCV in the immortalisation of B cells can be envisioned (Zignego 2000, Machida 2004).

Treatment of Lymphoproliferative Disorders

Because of the close correlation between the level of viral suppression and improvement of HCV-associated extrahepatic symptoms, the most effective antiviral strategy should be considered when dealing with HCV-related extrahepatic diseases. The protease inhibitors boceprevir and telaprevir have been shown to improve significantly sustained virologic response rate in HCV type 1-infected patients when given in combination with peg-interferon plus ribavirin as compared to peg-interferon and ribavirin alone, and can be therefore regarded as the treatment of choice in HCV type 1-infected patients with extrahepatic manifestations.

While asymptomatic **mixed cryoglobulinemia** *per se* does not constitute an indication for treatment, symptomatic mixed cryoglobulinemia should always be treated. Because asymptomatic cryoglobulinemia may evolve into symptomatic in the course of disease, vigilant monitoring is required and introduction of antiviral therapy in terms of prophylaxis should be considered. A therapeutic approach should primarily concentrate on the eradication of the virus. Clinical improvement of MC is reported in 50 to 70% of patients receiving antiviral therapy with IFN α and RBV and mostly correlates with a drastic reduction of HCV RNA concentrations (Calleja 1999). IFN α may lead to clinical amelioration even in virological nonresponders. Alternative therapeutic strategies such as cytostatic immunosuppresive therapy and/or plasmapheresis

should be considered (Craxi 2008) (Figure 7.2). Recent data show rituximab as an effective and safe treatment option for MC even in advanced liver disease. Moreover, B cell depletion has been shown to improve cirrhotic syndrome by mechanisms that remain to be further studied (Petrarca 2010).

In cases of severe **systemic vasculitis**, initial therapy with rituximab, a monoclonal chimeric antibody against CD20 B cell specific antigen, is suggested. A combined application of rituximab with PEG-IFN α plus ribavirin in cases of severe mixed cryoglobulinemia-related vasculitis resistant to antiviral therapy seems to be the optimal therapeutic strategy (Saadoun 2008). In severe rituximab-refractory mixed cryoglobulinemia-related vasculitis or acute manifestations, cycles of plasma exchange plus corticosteroids and eventually cyclophosphamide are indicated.

Low-dose interleukin 2 can lead to clinical improvement of vasculitis and has immunologic effects such as recovery of regulatory T cells (Saadoun 2011).

As eradication of *Helicobacter pylori* may lead to complete remission of MALT lymphoma, antiviral therapy can lead to regression of **low-grade NHL** in patients with HCV-related malignant lymphoproliferative disorders. PEG-IFN α plus ribavirin (+/- protease inhibitors) should be regarded as first line therapy (Giannelli 2003).

Treatment of HCV infected patients with **high-grade NHL** should be based on cytostatic chemotherapy. Current data suggest that antiviral treatment may serve as maintenance therapy for maintaining remission of NHL post-chemotherapy (Gianelli 2003).

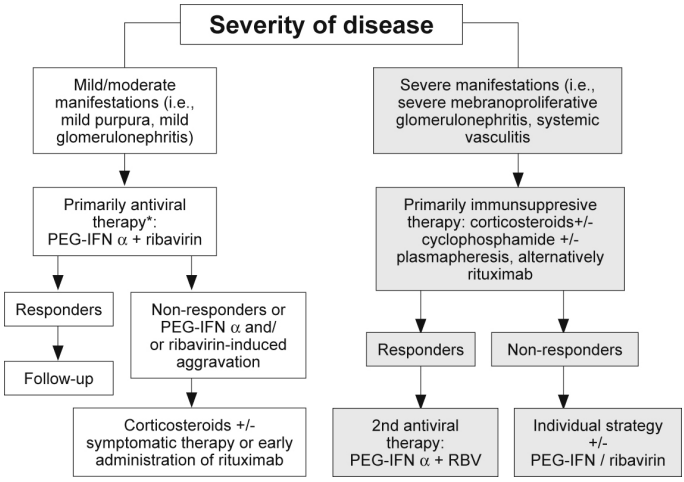

Figure 7.2 – Therapy algorithm for symptomatic HCV-related mixed cryoglobulinemia (modified from Craxi 2008). In patients with severe manifestations, treatment should focus on immunosupression with rituximab (± plasmapheresis).

Other Hematological Manifestations

Thrombocytopenic conditions are often observed in patients with chronic hepatitis C and result mainly from advanced liver fibrosis and manifest cirrhosis (Wang 2004). Along with classical therapeutic approaches such as corticosteroids, intravenous immunoglobulins and splenectomy, antiviral therapy constitutes another option. Caution is recommended with PEG-IFN α plus ribavirin as significant aggravation of HCV-related immune thrombocytopenic purpura may occur (Fattovich 1996). On the other hand, long-term use of steroids and immunosuppressive drugs is limited by an increased risk of fibrosis progression and a substantial elevation of virus. Eltrombopag may be an option. In case of refractory disease or aggravation during the course of antiviral therapy, rituximab should be considered (Weitz 2005).

Autoimmune hemolytic anemia (AHA) has been frequently observed in HCV patients treated with IFN α with and without

ribavirin and consequently recognized as a possible side effect of antiviral treatment (Nomura 2004) although there is conflicting evidence for regarding AHA as a possible EHM of chronic HCV infection.

Glomerulonephritis (GN) constitutes a rare extrahepatic complication of chronic HCV. Predominant manifestations are cryoglobulinemic or non-cryoglobulinemic membranous proliferative GN and mesangioproliferative GN. GN prevalence in HCV patients is estimated at 1.4% and is comparably high due to its prevalence among blood donors (Paydas 1996).

Patients with HCV-related GN should be primarily treated with antivirals. PEG-IFN and ribavirin dosage must be cautiously adjusted to glomerular filtration rate (GFR), in order to prevent mainly ribavirin accumulation and a resulting hemolytic anemia (Fabrizi 2008).

Fulminant manifestations with impending acute renal failure make administration of corticosteroids, immunosuppressive drugs such as cyclophosphamid and eventually plasmapheresis necessary (Garini 2007, Margin 1994). In cases of simultaneous bone marrow B cell infiltration and/or resistance to conventional therapy, application of rituximab is indicated (Roccatello 2004). ACE inhibitors or AT1 receptor antagonists are supplemental (Kamar 2006). About 13% of HCV-infected patients have **hypothyroidism** and up to 25% have thyroid antibodies (Antonelli 2004). There is evidence that IFN α may induce thyroid disease or unmask preexisting silent thyroidopathies (Graves disease, Hashimoto thyroiditis) (Prummel 2003). Some studies suggest that thyroid autoimmune disorders were significantly present in patients with chronic hepatitis C during but not before IFN α therapy (Vezali 2009). Monitoring of the thyroid function should be performed during treatment.

A meta-analysis of retrospective and prospective studies confirms a high risk for the development of **diabetes mellitus type II** in patients with chronic HCV infection (White 2008). Insulin resistance represents an independent risk factor for

progression of liver fibrosis in patients with chronic HCV infection (Moucari 2008).

Dermatologic and Other Manifestations

Table 7.3 – Overview

Manifestation	Feature	Note
Porphyria cutanea tarda	Correlated with HCV	Geographic distinctions
Lichen planus	Associated with HCV	Geographic distinctions/HLA-DR6
Idiopathic pulmonary fibrosis	Potential EHM	
Chronic alveolitis	Correlated with IFN treatment	
Ischaemic and hemorhagic strokes	Younger HCV patients	
Transverse myopathies/ symmetrical parapesis/ sensory deficiency	HCV	
Chronic fatigue/subclinical cognitive impairment/ psychomotor deceleration	35-68% of HCV patients	
Depression	2-30% of HCV patients	Perry 2008, Forton 2003
Altered neurotransmission	HCV	Weissenborn 2006
Tryptophan deficiency – depressive disorders	HCV/lack of serotonin	
Chronic myocarditis/ dilatative/hypertrophic cardiomyopathy	Genetic/immunologic factors	Matsumori 2000

8. Management of HCV/HIV Coinfection

Christoph Boesecke, Stefan Mauss and Jürgen Kurt Rockstroh

Epidemiology of HIV/ HCV Coinfection

Of the 33.4 million HIV-infected persons worldwide in 2009 it is estimated that at least 5 million of them had hepatitis C virus infection. Whereas both viruses are transmitted with high efficacy via blood-to-blood contact, HCV is less easily transmitted sexually. Thus, the prevalence of hepatitis C coinfection within different countries, regions and populations is closely related to the prevalence of blood-borne transmission (mainly intravenous drug use) of HIV (Table 8.1).
HCV may well be sexually transmitted and should therefore also be taken into account at regular STD screenings (Gotz 2005, Danta 2007, Vogel 2009a, Vogel 2010). HCV is detected in 4-8% of infants born to HCV-infected mothers (Bevilacqua 2009). However, in HIV/HCV-coinfected mothers receiving HAART and undergoing cesarean section the risk of HCV transmission is reduced to less than 1%. The average estimated risk of transmission for hepatitis C in HIV is depicted in Table 8.2.

Table 8.1 – Geographic differences in coinfection rates.

	HIV/HCV coinfection rates
Europe, Australia	25%
Belorus, Ukraine	70%
Belgium, Austria, Germany	10-15%
Australia, UK	10-15%
US general population	18-25%
US prison population	65-70%
Chinese blood donors	85%
Thailand	10%
Sub-Saharan Africa	Relatively low

Table 8.2 – Average estimated risk of transmission for HIV, HCV and HCV/HIV coinfection.

Mode of transmission	HIV	HCV	HCV/HIV coinfection
Perinatal	7-50%	1-7%	1-20%
Sexual contact*	1-3%	<1%	<4%
Needlestick injury	0.3%	<1%	Unknown

*With sexual contact the risk refers to cumulative exposure.

Diagnosing HCV in HIV Coinfection

The presence of HCV can be confirmed serologically by the detection of antibodies with ELISA testing. Loss of HCV antibodies does not necessarily indicate viral clearance (Cribier 1995). One negative HCV antibody ELISA does not necessarily exclude HCV infection in HIV-positive patients, especially in severe immune deficiency. A rise of liver transaminases has been proven to be more sensitive in the detection of acute HCV infection in HIV-positive patients than repeated testing for HCV antibodies (Thomson 2009).

The levels of HCV viremia increase eight times faster in HIV-positive individuals than in patients with hepatitis C who are not infected with HIV. The highest concentrations for HCV viremia have been reported in patients who subsequently develop liver

failure. Regular monitoring of HCV RNA levels is warranted in HIV/HCV-coinfected patients.

The Natural History of Hepatitis C in HIV+ Patients

Various studies have demonstrated that underlying HIV infection weakens the immune response to hepatitis C. Interestingly, data in HIV-positive individuals suggest that despite underlying HIV infection spontaneous resolution of HCV may occur in up to 20-30% of newly infected patients (Vogel 2010, Thomson 2011). Recently described single nucleotide polymorphisms (SNP) near the IL28B gene encoding for interferon lambda may explain the differences in spontaneous clearance rates between ethnicities (Clausen 2011, Thomas 2009). Numerous large cohort studies have demonstrated that once chronic hepatitis C is established the presence of HIV leads to a faster HCV clinical progression due to the lack of critical CD4+ T cell responses against HCV (Danta 2008).

In addition, within 10-15 years of HCV infection, 15-25% of HIV-coinfected patients develop cirrhosis compared with 2-6% of HIV-negative patients (Soto 1997). Mortality due to advanced liver disease starts ten years earlier in coinfected hemophiliacs than in HIV-negative hemophiliacs with hepatitis C (Darby 1997). The incidence of hepatocellular carcinoma is also higher in HIV-coinfected patients (Giordano 2004).

Effect of Hepatitis C on HIV Infection

Updated information from an analysis of the large EuroSIDA cohort, after taking into account ongoing chronic and resolved hepatitis C infection, confirm that no difference in CD4 cell count recovery is observed in patients with chronic hepatitis C infection and detectable HCV RNA in comparison to HIV-monoinfected patients (Rockstroh 2005). In addition, data from the same cohort revealed that CD4-positive T cell recovery in HIV-positive patients with maximal suppression of HIV

replication is not influenced by HCV serostatus, HCV genotype or level of HCV (Peters 2009).

Effect of HAART on Hepatitis C

There is increasing evidence that HAART-induced immune reconstitution might reverse the accelerated course for hepatitis C in patients with severe HIV-associated immune deficiency (Verma 2006, Vogel 2009b). Several cohort analyses show that HIV/HCV-coinfected individuals on HAART had significantly lower liver-related mortality than patients receiving either suboptimal or no antiretroviral therapy (Qurishi 2003).

The EACS antiretroviral treatment guidelines recommend earlier initiation of antiretroviral therapy in HIV+ patients with HCV coinfection (CD4+ cell count between 350-500/µl in asymptomatic patients). Various studies have shown that the presence of HCV is independently associated with an increased risk of rises in serum aminotransferases, highlighting the need for close monitoring.

Treatment

Once viral clearance is achieved with hepatitis C combination therapy, the prognosis of liver disease dramatically improves, and once HCV infection is eradicated, further liver complications are very unlikely. The goal of hepatitis C treatment is to achieve persistently negative HCV RNA levels. Pegylated interferon plus ribavirin is considered standard therapy in coinfected patients.

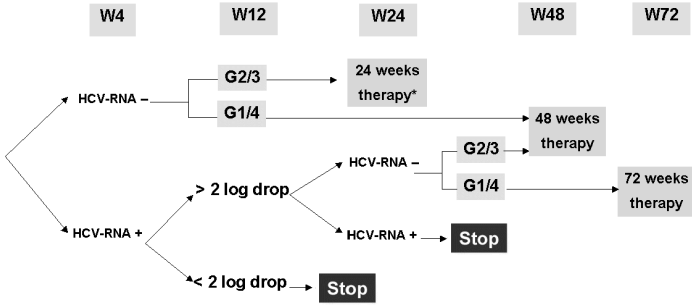

Figure 8.1 – Algorithm for management of hepatitis C in HIV coinfection. Proposed optimal duration of HCV therapy in HIV/HCV-coinfected patients (W: week; G: genotype) (modified from Rockstroh 2009a).

*In patients with low baseline viral load (<400,000 IU/l) and minimal liver fibrosis.

Noninvasive markers such as blood tests or transient elastography constitute a new means of assessing liver disease in HIV and hepatitis-coinfected individuals (Rockstroh 2009b, Resino 2011). When liver biopsy or non-invasive tests for assessing hepatic fibrosis (e.g., elastometry by Fibroscan®) demonstrate lower grades of liver fibrosis (F0-F1) regardless of HCV genotype, treatment may be deferred. Assessment of fibrosis should be repeated frequently to monitor progression in these cases. If chronic hepatitis C is detected early in the course of HIV infection (before the initiation of HAART), treatment for chronic HCV is advised. However, if a coinfected patient has pronounced immune deficiency (CD4 count <200 cells/ml), the CD4 count should be improved via HAART before beginning HCV treatment. Patients with a CD4 relative percentage of >25% are more likely to achieve SVR than those with lower CD4 percentages (Opravil 2008). If an early HCV RNA reduction of at least 2 $\log_{10}$ compared with baseline is not achieved by week 12, treatment should be discontinued.

Based on four baseline variables (serum HCV RNA, HCV genotype, liver fibrosis staging using elastometry, and IL28B

genotyping), the Prometheus index has been developed and can be used as a risk calculator for predicting the likelihood of SVR using PEG-IFN/ribavirin therapy in HIV-HCV-coinfected patients. It is freely available on the web (http://goo.gl/oPBJ9), like the Framingham score for predicting cardiovascular risk (EACS 2011).

With the registration of the first oral direct acting antivirals (DAAs), treatment recommendations for hepatitis C genotype 1 co-infected patients will change. So far, only interim data is available for both agents (24-week treatment response data) showing significantly higher rates of undetectable HCV RNA with triple therapy when compared with standard PEG-IFN plus ribavirin in coinfected patients, similar to the rates seen in Phase II and III trials in HCV monoinfection (Sherman 2011, Sulkowski 2011).

For fuller DAA updates, please see Chapters 4 and 5.

Antiretrovirals while on HCV therapy

Didanosine use has been independently associated with increased adverse event rates including lactic acidosis and hepatic decompensation in patients who have liver cirrhosis prior to commencement of PEG-IFN/RBV therapy (Mauss 2004). The use of AZT and d4T are also discouraged whenever possible, as increased toxicity can be expected.

Patients on atazanavir may develop jaundice due to an increase in total serum bilirubin levels following initiation of ribavirin (Rodriguez-Novoa 2008). The role of abacavir is uncertain at this point but cohort data suggest lower success rates (Bani-Sadr 2007). Table 8.4 summarizes possible interventions for HCV/HIV-coinfected non-responders and relapsers to previous interferon-based therapies.

When results of the currently ongoing pilot HIV/HCV coinfection studies are known, adding a DAA in G1 patients will become a new treatment standard.

Table 8.3 – Diagnostic procedures for hepatitis C in HIV coinfection (adapted from Rockstroh 2008).

Diagnosis of hepatitis C
HCV Ab (positive 1-5 months after infection, may rarely be lost with immunosuppression)
HCV RNA level* (while not prognostic for progression, it is for response to treatment)
Status of liver damage
Grading of fibrosis (e.g., Fibroscan®, liver biopsy, serum fibromarkers**)
Hepatic synthetic function (e.g., coagulation, protein, albumin, CHE)
Ultrasound and AFP every 6 months in cirrhotic patients (gastroscopy upon diagnosis of cirrhosis and every 1-2 years thereafter)
Before HCV treatment
HCV genotype and serum HCV RNA
Auto-antibodies (ANA, SMA, ANCA and LKM1***)
TSH, thyroid autoantibodies if applicable
Monitoring of HCV treatment
Differential blood count and liver enzymes every 2-4 weeks
HCV RNA at week 4 (to evaluate rapid virological response), week 12, 24, 48, (72 if applicable) and 24 weeks after stopping HCV therapy
CD4 count every 12 weeks
TSH every 12 weeks

*Low viral load defined as less than 400,000 IU/L when using PEG-IFN+RBV; there is no standard conversion formula for converting the amount of HCV RNA in copies/ml to the amount reported in IU. The conversion factor ranges between one and five HCV RNA copies per IU.

**Serum fibromarkers include APRI, FIB-4, hyaluronic acid, Fibrometer, Fibrotest, Forns, Hepascore and other indices; recently Fibrometer, Fibrotest and Hepascore have shown more accuracy in predicting liver fibrosis than simple biochemical tests such as APRI, FIB-4 or Forns.

***Patients with positive anti-LKM or -ANA with homogeneous pattern should be evaluated for concurrent autoimmune hepatitis especially in the presence of ALT elevation while on treatment.

Table 8.4 – Classification of and interventions for HCV/HIV-coinfected patients who are non-responders/relapsers to prior IFN-based therapies.

Category	Subgroup	Recommended Intervention
Suboptimal treatment	1. Suboptimal schedule - Interferon monotherapy - Low doses of ribavirin - Short length of therapy	Re-treatment using combination therapy of PEG-IFN plus weight-based dose of ribavirin
	2. Limiting toxicities & poor adherence	Optimal support (SSRI, paracetamol/NSAID*, adherence support, use of hematopoietic growth factors**)
Optimal treatment with virologic failure	1. Relapse (HCV RNA negative at the end of treatment)	Retreatment using combination therapy of PEG-IFN + weight-based RBV dosing (consider longer treatment duration)
	2. Non-response (no HCV RNA negativization during treatment)	Wait until new antivirals become available either through clinical trials or upon licensure

*NSAID, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitors.

**Data on the use of hematopoietic growth factors in HIV/HCV coinfection is limited to an improvement in quality of life but not antiviral efficacy; treatment with growth factors is generally off-label in Europe.

Liver Transplantation in HIV/HCV-Coinfected Patients

The presence of esophageal varices using upper gastrointestinal endoscopy should be monitored in patients with liver cirrhosis every 1-2 years; in addition, an ultrasound of the liver and a serum α-fetoprotein determination should be performed at least every 6 months in patients with F3/F4 fibrosis according to the European Consensus Guidelines (Alberti 2005).

For patients to be eligible for liver transplantation, they need to have either undetectable HIV viremia (<40 copies/ml) or at

least treatment options to control HIV infection successfully after liver transplantation. Contraindications for transplantation are opportunistic diseases, ongoing alcohol or drug abuse, HCC metastasis in other organs, a second malignant disease, cardiopulmonary disease, or older age with an elevated risk of mortality related to the operation.

Combination therapy with pegylated interferon plus ribavirin seems to be the best management option 1-3 months after liver transplantation and after reinfection with hepatitis C virus is detected.

In the context of post-transplant immunosuppression, it is important to point out that there are crucial pharmacokinetic drug-drug interactions between the key immunosuppressive drugs tacrolimus or cyclosporin A and the ARVs used for HIV therapy. Determinations of the plasma levels of the antiretroviral drugs are necessary. The doses of cyclosporin A or tacrolimus usually need to be reduced when the patient is treated concomitantly with a protease inhibitor, especially if boosted with ritonavir (Vogel 2004). By contrast, NNRTIs can lower the concentrations of immunosuppressive drugs.

Conclusion

Enhanced hepatotoxicity of HAART as well as drug-drug interactions between HAART and ribavirin clearly underline the need for specific treatment strategies. And as soon as SVR data from the pilot studies of DAAs in coinfected people are available, recommendations will change.

9. Management of HBV/HCV Coinfection

Carolynne Schwarze-Zander and Jürgen Kurt Rockstroh

Epidemiology

Due to shared routes of transmission, coinfection with HBV and HCV is not uncommon among individuals in HBV endemic areas who also have a high risk of parenteral infections, such as injection drug users (Pallas 1999), patients on hemodialysis (Reddy 2005), patients undergoing organ transplantation (Aroldi 2005) and HIV-positive individuals (Zhou 2007). Due to a lack of large-scale population-based studies the exact number of HBV/HCV coinfected patients is unknown. Dual infection with HBV and HCV in the same host ranges from 9% to 30% depending on the geographic region (Zarski 1998, Liaw 1995). These numbers may underestimate the true number of people with HBV/HCV coinfection as there is a well-known entity of occult HBV infection (i.e., patients with negative hepatitis B surface antigen [HBsAg] but detectable serum HBV DNA) in patients with chronic hepatitis C (Cacciola 1999).

Screening

Persons with a first episode of acute hepatitis should be screened for all viral causes including HBV and HCV (see Chapter 3). Some patients may be inoculated with both viruses simultaneously and will present with acute hepatitis due to both viruses. Superinfection of both viruses, on top of the other, has been reported (Liaw 2000, Liaw 2002, Liaw 2004). Episodes of acute hepatitis in patients with known chronic HBV or HCV infection should prompt screening for superinfection. In addition, in patients with chronic hepatitis C, ruling out occult HBV infection beyond HBsAg testing, i.e., by polymerase chain reaction (PCR), should be done when clinically indicated.

Viral Interactions

Coinfected patients may show a large spectrum of virologic profiles (Raimondo 2006). HCV infection can suppress HBV replication and it has been shown that HBV/HCV-coinfected patients have lower HBV DNA levels, decreased activity of HBV DNA polymerase, and decreased expression of HBsAg and hepatitis B core antigen in the liver (Chu 1998). Patients with chronic HBV infection who become superinfected with HCV can undergo seroconversion of HBsAg (Liaw 1991). HBV can inhibit HCV replication as well (Sato 1994). HBV DNA replication has been shown to correlate with decreased HCV RNA levels in coinfected patients (Zarski 1998).

Simultaneous suppression of both viruses by the other does occur (Jardi 2001). Thus, HBV or HCV can play the dominant role, HBV and HCV can inhibit each other simultaneously and they can alternate their dominance (Liaw 1995). Both viruses have the ability to induce seroconversion of the other. The chronology of infection may have a role in determining the dominant virus. The overall effect appears to be HCV suppression of HBV (Liaw 2001). Interestingly, recent *in vitro* studies found no evidence of direct interference between the two viruses, making interindividual differences in innate and/or adaptive host

immune responses responsible for viral interference observed in coinfected patients (Bellecave 2009, Eyre 2009).

Acute simultaneous coinfection with HBV and HCV is rarely seen, but the interaction of HBV and HCV appears to be similar to chronic infection. In acute infection with HBV and HCV, patients show delayed HBsAg appearance and a shorter hepatitis B surface antigenemia compared to those with acute HBV alone (Mimms 1993). Biphasic alanine aminotransferase (ALT) elevation is found in some patients, although rates of viral clearance were similar to those in HBV- or HCV-monoinfected patients (Alberti 1995).

HCV superinfection is frequent in HBV endemic areas, such as in Asia, South America and sub-Shaharan Africa (Liaw 2002, Liaw 2004), and can result in the suppression of HBV replication and termination of HBsAg carriage. Long-term follow-up analyses have described a higher rate of liver cirrhosis and hepatocellular carcinoma. Fulminant hepatic failure was significantly higher among patients with underlying HBV infection than those without (23% vs. 3%) (Chu 1999, Chu 1994).

HBV superinfection is less common in HCV-infected patients and very limited data is available. Superinfection of HBV may lead to suppression of HCV (Liaw 2000, Wietzke 1999). HBV superinfection may be associated with acute deterioration of liver function among patients with chronic HCV infection, and the risk of fulminant hepatitis may be increased (Sagnelli 2002).

Occult HBV infection, defined as detectable HBV DNA in liver or serum and undetectable HBsAg (Ozaslan 2009, Torbenson 2002), has been identified in up to 50% of patients with chronic HCV. A relation to HCV treatment outcomes has been described (Zignego 1997, Fukuda 2001, Sagnelli 2001). HCV infection with occult HBV infection has been associated with higher ALT levels, greater histological activity index and liver disease more often progressing to liver cirrhosis (Fukuda 1999, Cacciola 1999, Sagnelli 2001).

Patients with **chronic hepatitis** and concurrent detectable serum HBV DNA and HCV RNA are at highest risk of progression

to cirrhosis and liver decompensation and therefore should be considered for treatment (Table 9.1). Active HCV infection (HCV RNA+) in the setting of inactive HBsAg (HBsAg+/HBV DNA-) behaves similarly to HCV monoinfection. Another possibility is active HBV infection in patients with inactive or prior HCV infection (HBV-DNA +/HCV-RNA-/anti-HCV+). This immune profile is less common, and may indicate HBV suppression of HCV. Close follow-up of levels of viremia is needed for correct diagnosis and decision on the probably most successful treatment.

Table 9.1 – Immune profiles in HBV/HCV-coinfected patients with chronic hepatitis.

	HBV and HCV active	Occult HBV in chronic active HCV	HCV active in HBs Ag carrier
HBsAg	+	-	+
HBV DNA	+	+	-
Anti-HCV	+	+	+
HCV RNA	+	+	+

Higher rates of **cirrhosis** and more **decompensated liver disease** are found in HBV/HCV-coinfected patients compared to HBV-monoinfected patients (Fong 1991) and HCV-monoinfected patients (Mohamed Ael 1997). The incidence of **hepatocellular carcinoma** (HCC) was three times as likely in HCV/HBV-coinfected patients than in HBV- and twice as likely in HCV-monoinfection. The cumulative risk of developing HCC after 10 years was 45% in HBV/HCV-coinfected patients compared with 16% in HBV and 28% in HCV monoinfected patients (Chiaramonte 1999). HBV/HCV-coinfected patients should undergo a screening routine for HCC with liver ultrasound and α-fetoprotein levels in serum at least every 6 months.

Treatment

Generally, treatment guidelines for monoinfected patients should be applied to coinfected patients. In patients with HBV/HCV coinfection, treatment should be initiated when inclusion criteria for standard treatment guidelines of HBV and HCV monoinfection are met (see Chapters 4 and 5). As with HBV and HCV monoinfection, treatment of coinfected patients should be started in patients with active chronic hepatitis or cirrhosis before liver decompensation. Due to the variety of virological profiles in HBV/HCV coinfection it is important to assess the dominant virus prior to initiating therapy.

In coinfected patients with dominance of HCV infection, IFN plus ribavirin has been well-studied and proven efficient. The combination of PEG-IFN α-2b plus ribavirin was found to induce a sustained HCV RNA response in up to 93% (88% in HCV genotype 1 and 100% in genotype 2 and 3) of coinfected patients (Potthoff 2008). Close monitoring of both viruses is recommended during and after combination therapy. In patients with dominance of HBV disease, IFN +/- HBV polymerase inhibitor is a possible option. Until now most data available are for lamivudine. There is very little experience with other anti-HBV agents. Future studies are needed to assess the safety and effectiveness of antiviral therapy with pegylated interferon, ribavirin in combination with the newer nucleoside or nucleotide analogues such as adefovir, entecavir, telbivudine and tenofovir, that is, those with a higher genetic barrier.

Conclusion

No treatment standard has been established for HBV/HCV-coinfected patients. Treatment decisions must be made based upon identification of the dominant virus. Recent studies indicate that in patients with dominant HCV replication pegylated IFN plus ribavirin should be the treatment of choice. Although no treatment experience with the new DAA agents has been reported yet, their eventual availability will open new

pathways in treatment, which can be replicated in HBV/HCV coinfection. Patients with dominant HBV disease should be treated with nucleoside or nucleotide analogues alone or in combination with pegylated interferon and ribavirin. Caution must be exercised in treating coinfected patients, as flares of the untreated virus may occur.

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ISBN 978-3-942687-11-9