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Short Guide to Hepatitis C

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edited by
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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 **2013 Short Guide to Hepatitis C**, which is an expansion and update of the HCV chapters in **Hepatology – A Clinical Textbook** (2013), 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 2013

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Abbreviations

ADV: adefovir dipivoxil
AHA: autoimmune haemolytic anaemia
ALT: alanine aminotransferase
AST: aspartate aminotransferase
BID: twice a day
BOC: boceprevir
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: telaprevir
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 of 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 prevalence is significantly higher than in North America and Europe (CDC 2012). 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. Recent numbers from Europe still show an ongoing epidemic of acute HCV especially among IVDU and MSM (Rockstroh 2012).

Transmission

Parenteral exposure to hepatitis C 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, 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, Rockstroh 2012).

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 (Sarrazin 2010).

Acute hepatitis

After HCV inoculation, there is a variable incubation period. HCV RNA in blood (or the 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, such as the IL28B polymorphism.

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).

However, the best way to slow down liver fibrosis is successful treatment of HCV (van der Meer 2012). The new directly acting antivirals (DAA), with high efficacy and increasingly improving safety profiles, can greatly contribute to lowering the disease

burden caused by chronic HCV infection if we can identify infection earlier.

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

HCV is a small-enveloped virus with one single-stranded positive-sense RNA molecule of approximately 9.6 kb. It is a member of the *Flaviviridae* family. This viral family contains three genera – flavivirus, pestivirus, and hepacivirus. To date, only three members of the hepacivirus genus have been identified. HCV, GB virus B (GBV-B), and the recently detected canine hepacivirus (CHV) (Kapoor 2011). 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 dimers 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.

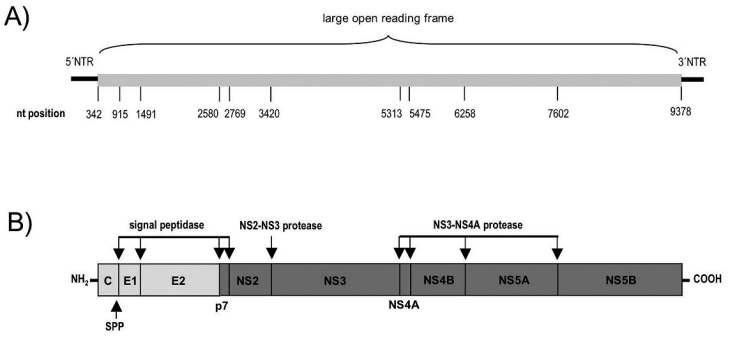

Figure 2.1 – Genome organization and polyprotein processing
A) Nucleotide positions correspond to the HCV strain H77 genotype 1a, accession number NC_004102. nt, nucleotide; NTR, nontranslated region. B) Cleavage sites within the HCV precursor polyprotein for the cellular signal peptidase, the signal 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 the 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 analyze in detail the different steps of viral replication (Figure 2.2).

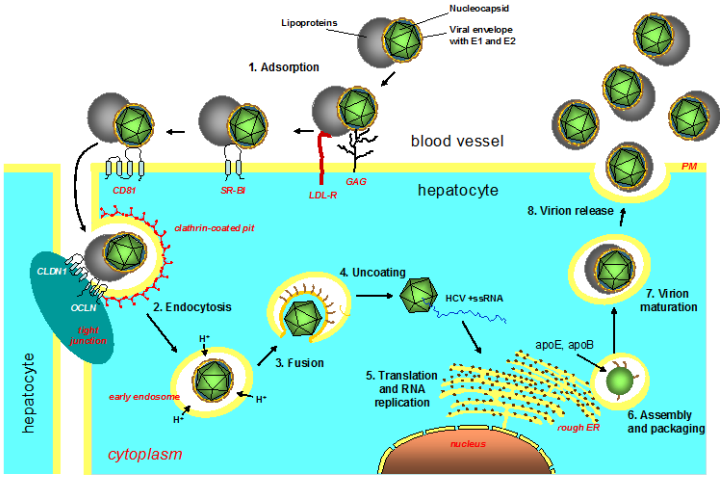

Figure 2.2 – Model of the HCV lifecycle. Designations of cellular components are in italics. For a detailed illustration of viral translation and RNA replication, see Pawlotsky 2007. HCV +ssRNA, single stranded genomic HCV RNA with positive polarity; rough ER, rough endoplasmic reticulum; PM, plasma 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). Finally, it has been shown that two receptor tyrosine kinases (RTKs) and the Niemann–Pick C1-like 1 (NPC1L1) cholesterol uptake receptor are cellular cofactors for HCV entry into hepatocytes (Lupberger 2011, Sainz 2012). 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 need to be investigated further.

Translation and post-translational 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 post-translationally 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 has been 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 results may occur in patients on hemodialysis or in severely immunosuppressed patients or those with 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 are being 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) 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). 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 standardized 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.

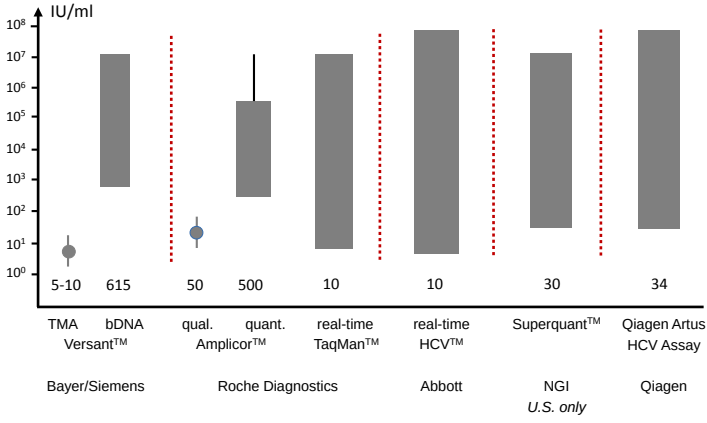

Figure 3.1 – Detection limits and linear dynamic ranges of commercially available HCV RNA detection assays

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 standardization (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).

HCV genotyping

HCV is heterogeneous with an enormous genomic sequence variability due to its rapid replication cycle producing 10^{12} virions a day and the 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 yet to come, HCV subtype determination will help to reveal possible barriers to resistance. Both direct sequence analysis and reverse hybridization 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 appears to be highly important in direct-acting antiviral agent (DAA) therapy because some HCV subtypes

(especially 1a vs 1b) behave differently regarding 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 standardization 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, which results, at least for telapravir, in a higher proportion of patients with negative HCV RNA and shortened treatment duration compared to the RealTime™ assay (lower limit of quantification 12 IU/mL) (Fevery 2012).

Outlook

It can be anticipated that in the near future many patients will be treated with interferon-free or interferon α-based combination therapies including two or more DAAs. For the success of such regimens, a thorough determination of novel algorithms to define treatment duration, treatment failure, or the selection of optimal regimens for individual patients will be crucial. Careful monitoring of antiviral resistance development will be decisive. Currently, resistance testing is still a domain of research using “home-brew” assays, but commercially available assays can be expected in the near future.

4. Standard Therapy of Chronic Hepatitis C Virus Infection

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Goal of antiviral therapy

The goal of antiviral therapy is to cure hepatitis C via a sustained elimination of the virus. A sustained elimination of HCV is achieved if the HCV RNA remains negative six months after the end of treatment (sustained virological response, SVR) (Table 4.1). Follow-up studies document that more than 99% of patients who achieve an SVR remain HCV RNA negative 4-5 years after the end of treatment and no signs of hepatitis have been documented (Manns 2008, Swain 2010). Importantly, long-term benefits of SVR are the reduction of HCV-related hepatocellular carcinoma and overall mortality (Backus 2011, Veldt 2007, van der Meer 2013). In 2011, the FDA accepted SVR-12 as endpoint for future trials because HCV relapse usually occurs within the first 12 weeks after the end of treatment. However, virologic relapses at later time points may appear in rare cases (Lawitz 2012).

In addition to liver disease, several other hepatic manifestations such as cryoglobulinemia, non-Hodgkin's

lymphoma, membranoproliferative glomerulonephritis or porphyria cutanea tarda have been reported in the natural history of hepatitis C virus infection (HCV). Antiviral treatment may improve symptoms even if an SVR is not acheived. On the other hand, antiviral therapy may worsen extrahepatic manifestations (Pischke 2008, Zignego 2007).

Basic therapeutic concepts and medication

Before the identification of HCV as the infectious agent for non-A, non-B hepatitis (Choo 1989), interferon α (IFN) led to a normalisation of transaminases and an improvement of liver histology in some patients (Hoofnagle 1986). After the identification of HCV it became possible to measure success of therapy as the long-lasting disappearance of HCV RNA from serum, the SVR. Since then, SVR rates have increased from 5-20% with IFN monotherapy up to 40-50% with the combination of IFN + ribavirin (RBV) (McHutchison 1998, Poynard 1998). Different HCV genotypes (HCV GT) show different SVR rates. Patients with the most frequent HCV GT1 require a longer treatment duration and still get a lower SVR compared to HCV GT2 and HCV GT3 (Figure 4.1). The development of pegylated interferon α (PEG-IFN) improved the pharmacokinetics of IFN, allowing more convenient dosing intervals and resulting in higher SVR, especially for HCV GT1. 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).

The two PEG-IFNs do have different pharmacokinetic profiles due to their different polyethylene glycol moieties. PEG-IFN α-2b is bound to a single linear 12 kDa polyethylene glycol molecule, whereas PEG-IFN α-2a is covalently attached to a 40 kDa branched chain polyethylene glycol moiety. The distinct sizes of

the PEG-IFN influence the volume of distribution. PEG-IFN α-2b is dosed according to body weight (1.5 µg/kg once weekly), while the larger PEG-IFN α-2a is given in a fixed dose of 180 µg once weekly (reviewed in (Cornberg 2002)) (Table 4.2). PEG-IFN α-2b may also be dosed at 1.0 µg/kg once patients become negative for HCV RNA, without major declines in SVR rates (Manns 2011a, McHutchison 2009b). RBV should be administered according to the bodyweight of the patient. A retrospective analysis of the large PEG-IFN α-2b + RBV pivotal trial revealed that the optimal dose of RBV (Rebetol®, Merck) is at least 11 mg/kg (Manns 2001). A prospective, multicentre, open-label, investigator-initiated study confirmed that PEG-IFN α-2b plus weight-based RBV is more effective than flat-dose ribavirin, particularly in HCV GT1 patients (Jacobson 2007). A RBV dose of 15 mg/kg would be ideal, although higher doses are associated with higher rates of anemia (Snoeck 2006). When combined with PEG-IFN α-2a, a RBV dose of 1000 mg if <75 kg or 1200 mg if ≥75 kg is recommended for HCV GT1 patients while a flat dose of 800 mg RBV was initially suggested for patients with HCV GT2 and 3 (Hadziyannis 2004). However, a weight-based dose of ribavirin (12-15 mg/kg) may be preferred, especially in difficult-to-treat patients and in response-guided therapy (RGT) approaches (EASL 2011, Sarrazin 2010). In 2011, the first direct antiviral agents (DAA) were approved for patients with HCV GT1. 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 GT1 patients (Jacobson 2011b, Poordad 2011b) and 29-88% in treatment-experienced HCV GT1 (Bacon 2011, Zeuzem 2011). However, both PIs require combination with PEG-IFN + RBV because monotherapy results 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 (Sarrazin 2012).

Table 4.1 – Relevant definitions for HCV treatment

Abbreviation	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)	Non-response (boceprevir)	HCV RNA ≥100 IU/mL at week 12; or HCV RNA positive at week 24, futility rule for BOC
NR (TLV)	Non-response (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

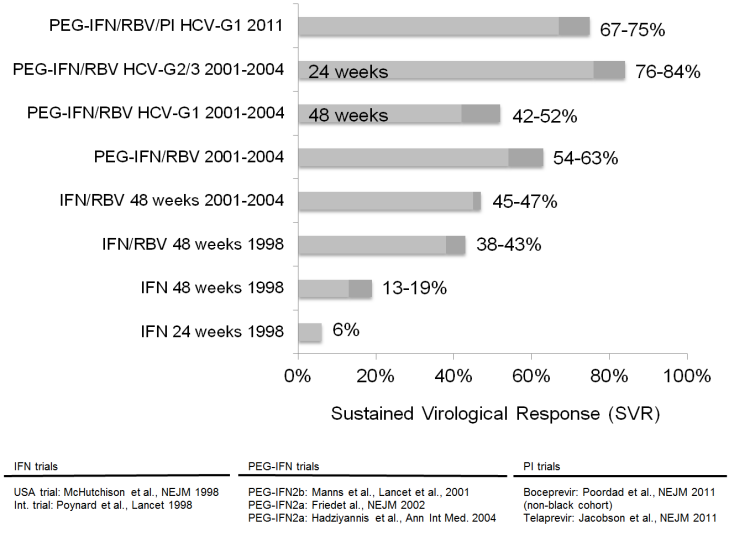

Figure 4.1 – Development of chronic hepatitis C therapy. The sustained virologic response rates have improved from around 5% with interferon monotherapy in the early 90s to >70% today with triple therapy of PEG-IFN + ribavirin + PI (data for treatment-naïve patients)

Predictors of treatment response

During the last decade, tailoring treatment duration and dosing according to individual parameters associated with response has 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).

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 IU three times weekly
Interferon α-2b (Intron A®)	3 Mill IU 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
Telaprevir (Incivek®, Incivo®)	750 mg (2 x 375 mg tablets) every 7-9 hours* *3 x 375 mg every 12 hours is as effective in treatment-naïve patients (Buti 2012)

On the other hand, new parameters seem to be more important such as HCV subtypes 1a and 1b. Patients with HCV GT1a have a higher risk of developing resistance during PI-based therapy compared to HCV GT1b because HCV GT1a requires an exchange of only one nucleotide versus two for HCV GT1b at position 155 to develop resistance (reviewed in Sarrazin and Zeuzem 2010b).

During treatment, the kinetics of the HCV RNA decline is a strong predictor of response. HCV RNA measurements at weeks 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 GT1 patients (Ge 2009, Rauch 2010, Suppiah 2009, Tanaka 2009) but also to a lesser extent for HCV GT2/3 (Mangia 2010c, Sarrazin 2011b). Data on IL28B explain the different responses to PEG-IFN/RBV between ethnic groups, i.e., the low SVR in African Americans and the high SVR in Asian patients. 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) (Poordad 2012) 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 2012). 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). Additional predictive markers are being evaluated. For example, low serum levels of interferon γ inducible protein 10 (IP-10) are associated with SVR and may improve the predictive value for discrimination between SVR and non-response (Darling 2011, Fattovich 2011).

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 developed resistance within a few days (Sarrazin 2007). RAVs associated with resistance to BOC and TLV are listed in Table 4.3. 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 does not make sense. As mentioned above, combination with 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 will 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 within 1-2 years after the end of therapy (Sarrazin 2007, Sherman 2011b). At this stage there is no rationale to routinely analyse HCV sequences either before therapy or during treatment because it has no practical consequence. Dominant RAVs before treatment have been documented (Kuntzen 2008) but the influence of treatment response is not well characterised.

Table 4.3 – Resistant-associated amino acid variants of HCV NS3 protease to boceprevir and telaprevir (adapted from Sarrazin 2012)

	V36A /M	T54S /A	V55A	Q80R /K	R155K /T/Q	A156S	A156T /V	D168A /E/G/ H/T/Y	V170A /T
BOC	X	X	X		X	X	X		X
TLV	X	X			X	X	X		

Treatment of HCV genotype 1

Treatment of naïve patients

Untreated patients with HCV genotype 1 (HCV GT1) have various treatment options. Triple therapy with PEG-IFN+RBV+PI increases the overall SVR by 25-31% (Table 4.4). 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 4.2A, 4.2B), 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 can achieve high SVR without adding a PI. Patients with low viral load at baseline who achieve an 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) (Table 4.5). One prospective trial confirmed that 24 weeks of dual therapy is not inferior compared to 28 weeks PEG-IFN/RBV/BOC in patients with low viral load and RVR (Pearlman 2012). 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 an SVR when they add BOC. Other negative predictors (HCV GT1a, cirrhosis) together with the lead-in concept may increase the negative predictive value of achieving an 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. The lead-in concept was developed in the BOC studies with the hypothesis of reducing resistance and improving SVR (Kwo 2010). However, the lead-in seems to have no significant effect on the SVR or on the development of antiviral resistance (Kwo 2010, Zeuzem 2011). Lead-in has also been evaluated for TLV but only in treatment-experienced patients (Zeuzem 2011). It is recommended to discuss the lead-in option and the consequences with the patient before initiation of treatment.

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

Study	Dosing	eRVR, SVR
SPRINT-2 (Poordad 2011b) n=938 non-black (NB) n=159 black *28 weeks if eRVR BOC	a) 1.5 μg/kg PEG-IFN α-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 α-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 α-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 α-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 α-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 α-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 α-2a, 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 α-2a, 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 α-2a, 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 FDA, i.e., 79% SVR for telaprevir 12 weeks, PEG-IFN/RBV

Table 4.5 – High SVR in naïve patients with HCV genotype 1 and low baseline viral load treated with 24 weeks of PEG-IFN/RBV

Study	Treatment	Subgroups (fast responder)	Weeks	SVR
(Zeuzem 2006) n=235	1.5 µg/kg PEG-IFN α-2b 800-1400 mg ribavirin	<600,000 IU/ml TW0	24	50%
		<600,000 IU/ml TW0 & <29 IU/ml TW4 (RVR)	24	89%
(Berg 2009) n=433	1.5 µg/kg PEG-IFN α-2b 800-1400 mg ribavirin	<5.3 IU/ml TW4 (RVR)	18-24	80%
		<800,000 IU/ml TW0 & <5.3 IU/ml TW4 (RVR)	18-24	100%
(Sarrazin 2011a) n=398	1.5 µg/kg PEG-IFN α-2b 800-1400 mg ribavirin	<800,000 IU/ml TW0 & <5-10 IU/ml TW4 (RVR)	24	88%
(Jensen 2006) n=216	180 µg PEG-IFN α-2a or 800 mg or 1000-1200 mg ribavirin	<50 IU/ml TW4 (RVR)	24	89%
		>50 IU/ml TW4 (RVR)	24	19%
(Ferenci 2008) n=120	180 µg PEG-IFN α-2a or 1000-1200 mg ribavirin	<50 IU/ml TW4 (RVR)	24	74% ITT 79% PP
(Pearlman 2012) n=171	1.5 µg/kg PEG-IFN α-2b 1000-1200 mg ribavirin	Patients with <25 IU/ml TW4 (RVR) were randomized 1:1	24	89% Relapse 6%
	1.5 µg/kg PEG-IFN α-2b, 1000-1200 mg RBV 800 mg TID BOC (wk 4-28)		28	90% Relapse 3%

* SVR, sustained virologic response; RVR, rapid virologic response

Treatment regimens with boceprevir

Boceprevir (BOC) is a linear peptidomimetic ketoamide serine protease inhibitor that binds reversibly to the HCV non-structural 3 (NS3) active site. BOC results in a significant decline of HCV RNA but given as monotherapy leads to rapid emergence of viral resistance (Sarrazin and Zeuzem 2010b). Thus, combination with PEG-IFN/RBV is necessary (Mederacke 2009). 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 GT1 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 4.4) 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. Based on published data for response rates being lower for African-American patients, black and non-black patients were analysed as two different pre-defined cohorts in the SPRINT-2 study. Overall, adding BOC to PEG-IFN/RBV significantly improved SVR in previously untreated patients with HCV genotype 1 leading to approval in 2011 (FDA: May; EMA: July). Non-black patients achieved 27-28% higher SVR, black patients increased SVR by 19-30%.

The responsiveness to PEG-IFN/RBV is very important for the success of treatment with BOC. This is highlighted 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 demonstrate an SVR of about 80% if treated with BOC but only 28-38% responded if HCV RNA declined less than 1 $\log_{10}$. Thus, the lead-in phase can be valuable in predicting responsiveness to PEG-IFN/RBV for further individualization of therapy as discussed above (Figure 4.3). Importantly, the overall SVR rates between the RGT group and the fixed 48-week therapy group were comparable (Table 4.4). 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 4.2A) but the accepted treatment duration for BOC RGT is different than the definition within the Phase III study (32 vs 24 weeks BOC for patients without eRVR) (Figure 4.2A). In addition, futility rules on prescription information differ from those applied in the Phase III trials, i.e., there was no week 12 stopping criteria in the SPRINT-2 study, while patients were supposed to discontinue treatment if they had detectable HCV RNA at week 12 in the RESPOND-2 trial. None of the 65 patients with HCV RNA level >100 IU/ml at week 12 achieved SVR in the SPRINT-2 study (Jacobson 2012). However, 21 patients achieved SVR despite detectable HCV RNA but <100 IU/ml at week 12. Based on a retrospective analysis in a small number of patients, this supports the futility rule of >100 IU/ml at week 12. There is no week 8 stopping rule in the prescribing information for BOC, while comparable stopping criteria have been established for TLV (4 weeks of triple therapy). However, Phase III data provide some support for a stopping rule at week 8. A futility rule of <3 $\log_{10}$ decline at week 8 would have missed SVR in only 2/53 patients (Jacobson 2012). The question is whether achieving SVR in two more patients, while exposing 51 patients unnecessarily to four more weeks of triple therapy with the associated costs and AEs is reasonable. Treatment discontinuation could be discussed in these patients on an individual basis.

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 α-2a/RBV (Flamm 2011). Thus, both PEG-IFNs can be combined with BOC.

Treatment regimens with telaprevir

Telaprevir (TLV) is also an orally administered reversible, selective, peptidomimetic NS3/4A serine protease inhibitor, which leads to a significant decline of HCV RNA although viral

resistance emerges rapidly if given as monotherapy (Sarrazin 2007). Thus, 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. One prospective trial has demonstrated similar response rates with 750 mg three time a day or with 1125 mg twice daily in treatment-naïve patients (Buti 2012). If the twice-daily regimen has similar efficacy in difficult-to-treat patients such as patients with non-response or liver cirrhosis remains to be studied. 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 GT1 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 GT1 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 alone. Patients who achieved eRVR qualified for 24 weeks of therapy (Table 4.4). SVR was significantly higher among those receiving TLV compared to the placebo group; 12 weeks TLV resulted in the highest SVR (Table 4.4). In all treatment groups, more than 80% of patients who achieved eRVR attained 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 GT1 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 4.4) (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 GT1 patients without liver cirrhosis. Also, retrospective analysis of the data showed that early HCV RNA measurement at week 4 is predictive of non-response 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.

In contrast, some easy-to-treat patients may only require 12 weeks of treatment. A retrospective analysis of the PROVE2 study revealed that all 12 naïve patients with IL28B CC genotype without cirrhosis achieved SVR after 12 weeks of PEG-IFN/RBV/TLV (Bronowicki 2012).

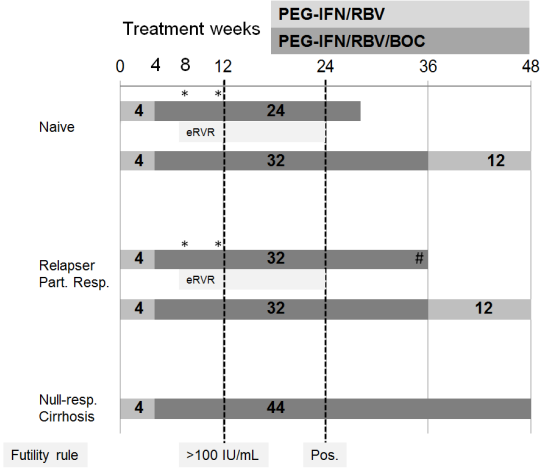

Figure 4.2A – Treatment with BOC/PEG-IFN/RBV: Approved treatment algorithm for HCV GT1 patients. *, RGT if eRVR (HCV RNA LLD week 8-24); #, EMA did not approve RGT for BOC regimens in previously-treated patients

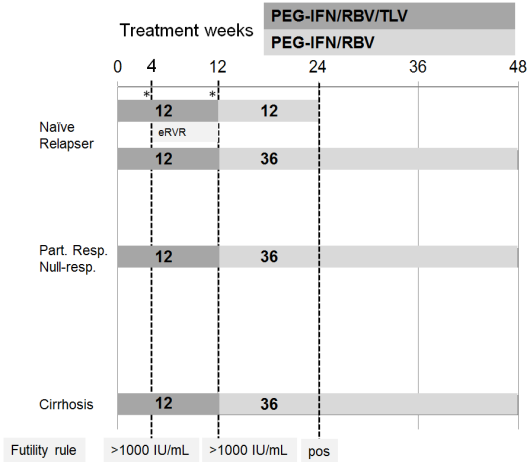

Figure 4.2B – Treatment with TLV/PEG-IFN/RBV: Approved treatment algorithm for HCV GT1 patients. *RGT if eRVR (HCV RNA LLD week 4-12) ***If patients have contraindications for BOC or TLV, dual therapy with PEG-IFN/RBV should be given for 24-72 weeks according to the HCV RNA decline at week 4 and week 12 (Sarrazin, Berg, Cornberg 2010 S3-Leitlinie). The treatment algorithm is similar to Figure 4.6

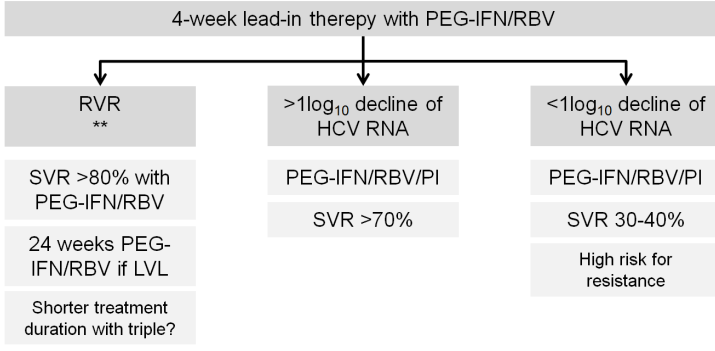

Figure 4.3 – Suggestion to use the lead-in strategy for individualisation of treatment in patients with HCV genotype 1. **The number of patients with low baseline HCV RNA and RVR may vary between different countries due to IL28B differences

Treatment of patients with prior antiviral treatment failure

As more patients have been treated, the size of the population of patients who have failed to achieve SVR with PEG-IFN/RBV has expanded. Many non-responder patients have advanced liver disease and successful treatment may extend life expectancy (Backus 2011, Veldt 2007, van der Meer 2012). Retreatment of patients with previous treatment failure is one of the most important current topics in the treatment of chronic hepatitis C.

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 (see Table 4.1, Figure 4.4).

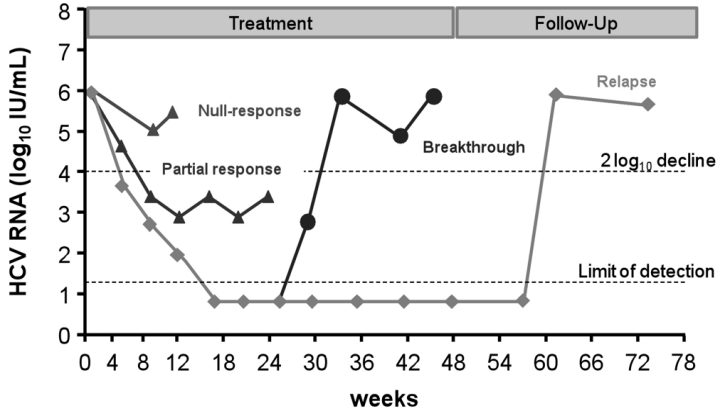

Figure 4.4 – Different scenarios of antiviral treatment failure in chronic hepatitis C

Retreatment of HCV GT1 patients with relapse after PEG-IFN/RBV

Retreatment with PEG-IFN/RBV of relapse patients after IFN/RBV or PEG-IFN/RBV 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 4.6). 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 4.2A, 4.2B) if cirrhosis is excluded (Ghany 2011, Sarrazin 2012). In contrast, 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 4.6).

Retreatment of HCV GT1 patients with previous partial response

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 4.6). FDA but not EMA approved RGT for BOC (Figures 4.2A, 4.2B). Treatment duration for PEG-IFN/RBV/TLV is 48 weeks for all PR patients (Figure 4.2B). 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 GT1 patients with previous null response

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 29-40% (Zeuzem 2011, Bronowicki 2012b) (Table 4.6). If further negative predictive factors are present, SVR decreases to 27% in HCV GT1a patients and to 14% in cirrhotic patients (not significantly different from PEG-IFN/RBV) (Figure 4.7A). 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 4.2A, 4.2B).

PEG-IFN maintenance therapy

There has been much interest concerning the use of low-dose PEG-IFN maintenance therapy in patients with a null response since data has suggested that IFN may halt progression of liver disease (Nishiguchi 1995). There are two major published trials that have analysed if maintenance treatment with IFN alters the natural course of chronic hepatitis C. In the EPIC[3] trial, non-responders to IFN/RBV with compensated cirrhosis and no evidence of HCC received 0.5 μg/kg PEG-IFN α-2b or no treatment for a maximum period of 5 years or until patients developed clinical events (hepatic decompensation, HCC, death, or liver transplantation). The study revealed no significant difference in time to first clinical event among patients who received PEG-IFN compared with controls (Bruix 2011).

The HALT-C trial, a long-term maintenance study supported by the National Institutes of Health evaluated a large cohort of chronic HCV-infected patients who had failed previous IFN-based therapy and had METAVIR stage F2-F4. Patients received 90 μg PEG-IFN α-2a maintenance treatment if they did not respond during the first 20 weeks with standard therapy. Despite the fact that there were greater reductions in viremia, decreases in alanine aminotransferase, and necroinflammation in the patients who received PEG-IFN, none of the important clinical outcomes (rates of death, decompensation, hepatocellular carcinoma, and increase in fibrosis) were favourably affected by PEG-IFN therapy (Di Bisceglie 2008). However, an extended analysis of the HALT-C cohort showed that patients with baseline cirrhosis who received PEG-IFN treatment had a slightly lower risk of HCC than controls (Lok 2011). The authors discussed that this marginal benefit does not justify maintenance treatment with PEG-IFN. In conclusion, long-term treatment with low-dose PEG-IFN cannot be recommended (Sarrazin 2010a).

Table 4.6 – 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 there were 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 α-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 α-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 α-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 α-2a, 1000-1200 mg RBV 48 weeks 44 weeks placebo (wk 4-48)	a) REL, PR: 21%
	b) 180 µg PEG-IFN α-2a, 1000-1200 mg RBV 48 weeks 44 weeks 800 mg TID BOC (wk 4-48)	b) REL, PR: 64%
PROVIDE (Bronowicki 2012b) n=49 (47 available)	1.5 µg/kg PEG-IFN α-2b, 600-1400 mg RBV 48 weeks 44 weeks 800 mg TID BOC (wk 4-48)	40% (19/47)
REALIZE (Zeuzem 2011) n=663	a) 180 µg PEG-IFN α-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 α-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 α-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%

Treatment of HCV genotypes 2 and 3

Naïve patients

TLV shows antiviral efficacy against HCV GT2 but is not effective against HCV GT3 (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 GT1. Thus, SOC for HCV GT2/3 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 GT2/3 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 GT2/3 patients may indeed be treatable for 12-16 weeks if certain prerequisites are fulfilled, especially the rapid virologic response (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) (Table 4.7).

In addition to the RVR, the specific HCV genotype and the baseline viral load are associated with response. Patients with GT2 respond better to PEG-IFN/RBV than those infected with GT3 (Zeuzem 2004b). Furthermore, the shorter treatment schedules reveal that HCV GT3 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 GT3 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).

Table 4.7 – Response-guided therapy for patients with HCV genotypes 2 and 3

Study	Treatment	Subgroups	Therapy weeks + SVR*	
(von Wagner 2005) n=153	180 µg PEG-IFN α-2a 800-1200 mg ribavirin	>600 IU/ml TW4	24	36%
		<600 IU/ml TW4	24	80%, 84% if HCV RNA<800,000 IU/ml
		<600 IU/ml TW4	16	82%, 93% if HCV RNA<800,000 IU/ml
(Shiffman 2007b) n=1469	180 µg PEG-IFN α-2a 800 mg ribavirin	All patients	24	70%
		All patients	16	62%
		<50IU/ml TW4 (RVR)	24	85%
		<50IU/ml TW4 (RVR)	16	79%
		<400,000IU/ml TW0 (LVL)	24	81%
		<400,000IU/ml TW0 (LVL)	16	82%
(Mangia 2005) n=283	1.0 µg PEG-IFN α-2b 1000-1200 mg ribavirin	Standard group	24	76%
		Standard group	24	91% if TW4 HCV RNA <50 IU/ml
		>50 IU/ml TW4 (no RVR)	24	64%
		<50 IU/ml TW4 (RVR)	12	85%
(Dalgard 2008) n=428	1.5 µg PEG-IFN α-2b 800-1400 mg ribavirin	<50 IU/ml TW4 (RVR)	24	91% ITT, 93% with F24 HCV RNA test
		<50 IU/ml TW4 (RVR)	14	81% ITT, 86% with F24 HCV RNA test
		>50 IU/ml TW4 (no-RVR)	24	55% ITT, 59% with F24 HCV RNA test
(Manns 2011a) n=682	1.0 µg PEG-IFN α-2b 1.5 µg PEG-IFN α-2b 800-1400 mg ribavirin	All patients	24 (1.5)	67% ITT, 82% as-treated
		All patients	24 (1.0)	64% ITT, 80% as-treated
		All patients	16 (1.5)	57% ITT, 68% as-treated

* SVR, sustained virologic response; RVR, rapid virologic response; LVL, low baseline viral load

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 GT2/3 undergoing short treatment (Mangia 2010b).

In contrast, GT2/3 patients who do not achieve RVR (especially HCV GT3 with high viral load) may be treated for longer than 24

weeks (i.e., 36-48 weeks) (Figure 4.5). However, most data are retrospective (Willems 2007). The prospective N-Core study investigated 24 weeks versus 48 weeks PEG-IFN α-2a/RBV. This study was prematurely terminated because of slow enrolment and could only show a significant difference in those patients who completed the study (73% versus 54% SVR), but not in the intent-to-treat analysis (Cheinquer 2012). A prospective study from Italy showed a numerically significant benefit of 36 weeks versus 24 weeks (75% vs. 62%) (Mangia 2010a). Depending on the assay used to determine RVR, around 25-30% of GT2/3 patients belong to this difficult-to-treat population not achieving RVR (Table 4.8). Tailoring treatments individually for patients with HCV G2/3 will reduce costs and side effects and further optimise the response rates.

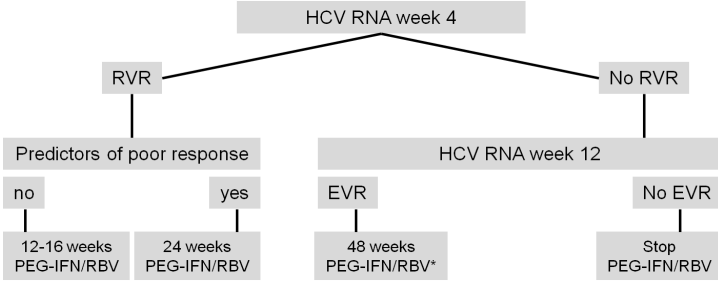

Figure 4.5 – Recommendation for treatment of HCV genotypes 2 and 3. Sensitive HCV RNA assays (limit of detection 12-15 IU/ml or 50 IU/ml) at weeks 4 and 12 may determine treatment duration. Reducing treatment duration is not recommended in patients with liver cirrhosis, insulin resistance, diabetes mellitus or hepatic steatosis

Table 4.8 – SVR of patients with HCV genotypes 2 or 3 not achieving RVR

Study	Frequency of patients without RVR	SVR without RVR (24 wks therapy)
(von Wagner 2005) 180 µg PEG-IFN α-2a 800-1200 mg ribavirin	7% (HCV RNA >600 IU/ml TW4)	24 weeks 36% SVR
(Shiffman 2007b) 180 µg PEG-IFN α-2a 800 mg ribavirin	36% (HCV RNA >50 IU/ml TW4) (24 wk group)	24 weeks 45% SVR
(Mangia 2005) 1.0 µg/kg PEG-IFN α-2b 1000-1200 mg ribavirin	36%-38% (HCV RNA >50 IU/ml TW4)	24 weeks 48%-64% SVR
(Dalgard 2004) 1.5 µg/kg PEG-IFN α-2b 800-1400 mg ribavirin	22% (HCV RNA >50 IU/ml TW4/TW8)	24 weeks 56% SVR
(Dalgard 2008) 1.5 µg/kg PEG-IFN α-2b 800-1400 mg ribavirin	29% (HCV RNA >50 IU/ml TW4)	24 weeks 55% SVR
(Cheinquer 2012) 180 µg PEG-IFN α-2a 1000-1200 mg ribavirin	n=188 patients with non-RVR were randomized for 24 versus 48 weeks	24 weeks 52% ITT SVR 24 weeks 54% SC SVR 48 weeks 61% ITT SVR 48 weeks 73% SC SVR

ITT: intention to treat, SC: study completers

Treatment of HCV GT2/3 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**)**. Non-responders can be retreated with an additional course of PEG-IFN/RBV. It is important to optimise dose and duration of treatment. HCV GT2 non-responders may benefit from retreatment with PEG-IFN/RBV/PI (data only for TLV). Triple therapy is off-label but may be considered in difficult-to-treat GT2 patients with an urgent treatment indication. Future DAAs will be pan-genotypic and therefore also effective for HCV GT3 (see Hepatology

Textbook, Chapter 13). Non-responder 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 GT3 (Bochud 2009).

Treatment of HCV genotypes 4, 5, and 6

BOC and TLV have hardly been tested in patients with HCV GT4, 5, or 6 and neither PI is approved for the treatment of GT4, 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 GT4, 5, and 6 and further large, prospective randomized studies with RGT are rare. Importantly, GT4, 5, and 6 are very common in areas where chronic hepatitis C is highly prevalent. For example, HCV GT4 is most prevalent in the Middle East and Egypt where it accounts for >80% of all HCV cases (approximately 34 million people) (Khattab 2011). HCV GT5 is most prevalent in South Africa, and genotype 6 in Southeast Asia (Nguyen 2005). Available study results, although limited, suggest that patients with HCV GT4, 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 GT4, 5 and 6 appear easier-to-treat compared to HCV GT1 but the optimal treatment duration is not clear (Antaki 2010, Nguyen 2005) (Table 4.9). Although some studies show SVR on the same order as for HCV GT2/3 patients, a fixed duration of 24 weeks of treatment as for GT2/3 is not advisable, even for patients with HCV GT6, which appears to show the best SVR (Lam 2010, Nguyen 2008). RGT based on early viral kinetics should be possible. Patients who achieve RVR are candidates for a short treatment regimen of 24 weeks if they do not have predictors of poor response (see above). Based on data for GT1 (Berg 2006, Sanchez-Tapias 2006), patients without RVR and/or partial

response may be considered for 72 weeks. This has been proposed for HCV GT4 by an international expert panel (Khattab 2011), but the evidence is limited. The proposed algorithm is shown in Figure 4.6. We suggest treating GT5 and 6 also according to this algorithm. Patients with treatment failure may be considered for retreatment, especially if the previous therapy was suboptimal. It is important to optimise dose and duration of treatment during retreatment.

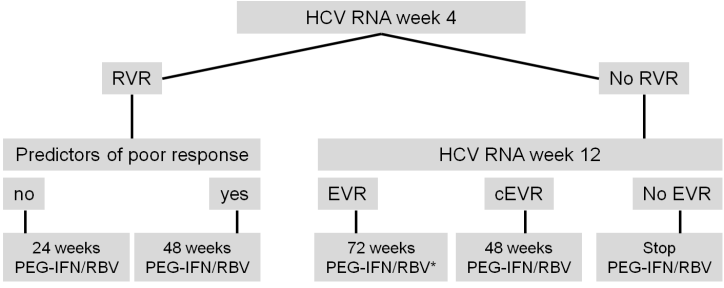

Figure 4.6 – Suggestion for treatment of HCV genotypes 4, 5, and 6. This algorithm was initially proposed for HCV GT4 (adapted Khattab 2011). Sensitive HCV RNA assays (limit of detection 12-15 IU/ml or 50 IU/ml) at weeks 4 and 12 may determine treatment duration. Reducing treatment duration is not recommended in patients with predictors of poor response (liver cirrhosis, insulin resistance, diabetes mellitus or hepatic steatosis, high baseline viral load >800,000 IU/mL)

Table 4.9 – Efficacy of antiviral treatment with PEG-IFN plus ribavirin in patients with chronic hepatitis C infected with genotypes 4, 5, and 6. Selected trials

Study	Treatment	HCV genotype /Duration		SVR
(Diago 2004) n=49	180 µg PEG-IFN α-2a 800/1000/1200 mg ribavirin	G4	24 weeks 24 weeks 48 weeks 48 weeks	0% (if low RBV) 67% (if high RBV) 63% (if low RBV) 79% (if high RBV)
(Hasan 2004) n=66	1.5 µg/kg PEG-IFN α-2b 1000/1200 mg ribavirin	G4	48 weeks 48 weeks 48 weeks	68% 55% (if HVL) 86% (if LVL)
(Kamal 2005) n=287	1.5 µg/kg PEG-IFN α-2b 1000/1200 mg ribavirin	G4	24 weeks 36 weeks 48 weeks	29% 66% 69%
(Kamal 2007) n=358	1.5 µg/kg PEG-IFN α-2b 10.6 mg/kg ribavirin RGT	G4	24 weeks RGT 36 weeks RGT 48 weeks RGT 48 weeks	86% (if RVR) 76% (if cEVR) 56% (if EVR) 58%
(Ferenci 2008) n=66	180 µg PEG-IFN α-2a 1000/1200 mg ribavirin RGT	G4	24 weeks RGT	87% (if RVR)
(Bonny 2006) n=59	PEG-IFN α-2a or b 800-1200 mg ribavirin	G5	48 weeks	58%
(Lam 2010) n=60	PEG-IFN α-2a 800-1200 mg ribavirin	G6	24 weeks 48 weeks	70% 79%
(Nguyen 2008) n=35	PEG-IFN α-2a or b 800-1200 mg ribavirin	G6	24 weeks 48 weeks	39% 75%

RBV, ribavirin; LVL, low baseline viral load; HVL, high baseline viral load; RGT, response-guided therapy

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). The definition of adherence used here is the "80/80 rule", that is, patients who receive more than 80% of the medication and are treated for more than 80% of the planned duration of treatment are considered adherent. One of the first studies investigating the effect of adherence in PEG-IFN/RBV treatment demonstrated that patients who fulfilled the 80/80 rule had a 63% SVR compared to 52% of those with less than 80% adherence (McHutchison 2002). Another study showed that a cumulative ribavirin dose of more than 60% is important to achieve an SVR (Reddy 2007). For the new triple therapy, adherence to the PI becomes even more important. The three-times-daily regimen necessitates highly-motivated and compliant 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 for managing 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

The management of side effects is one of the most important factors for the success of treatment and deserves its own chapter (Chapter 6).

Drug interactions

With the introduction of PIs to the treatment of chronic HCV infection a completely new challenge has to be faced: drug-drug interactions. BOC and TLV undergo extensive hepatic metabolism especially by the cytochrome P450 CYP3A pathway, which metabolizes more than 50% of clinically used drugs and is often involved in adverse drug interactions (Burger 2012). 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. In addition, both PIs are substrates and inhibitors of p-glycoprotein (P-gp) transport. Co-administration of TLV or BOC with drugs that are substrates for P-gp transport may result in increased plasma concentrations of such drugs, which could increase adverse reactions.

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. In some cases a closer monitoring or slight dose modifications may be sufficient while some drugs should be strictly avoided especially if alternatives are available that do not cause interactions. Furthermore, the patient has to be informed that he must not self-medicate since interactions are not limited to approved drugs. Even herbals and food have to be considered, as St. John's Wort is a potent inducer of CYP3A and naringin, a flavinoid of grapefruit, an inhibitor. A list of drug interactions is given in the official prospectus. 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 altered by more than 30%. The table *Overview of drug interactions of HCV PIs with frequently used comedication* (see http://hepatologytextbook.com/Table12_11.pdf) gives an overview about potential interactions of frequently used drugs and implications for management and alternative drugs.

Treatment of hepatitis C in special populations

Patients with acute hepatitis C

The goal of acute hepatitis C treatment is the prevention of persistent HCV infection. The natural rate of HCV evolution to a chronic state is 50-90%. As a vaccine is not yet available, early treatment of acute HCV infection with IFN is the only option to prevent persistent HCV infection; however, the diagnosis of acute primary HCV infection may be difficult and its distinction from exacerbation of an underlying unrecognized chronic HCV infection may be difficult (Sarrazin 2010a). 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). However, good patient adherence to therapy is necessary to achieve these response rates (Wiegand 2006). Co-administration with ribavirin does not seem to be necessary. This may be different in patients with HIV coinfection (Grebely 2011a) (see Hepatology Textbook, Chapter 17). 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. However, early treatment of acute HCV infection to prevent chronic disease does have its limitations. A main problem is that primary HCV infection is usually asymptomatic and most patients cannot be identified in this early stage of disease. Another reason is that a number of patients have medical contraindications for treatment with IFN or are not ready for therapy because they are still active intravenous drug users (IDU).

There are two concerns in treating active IDU with IFN. In case of successful therapy there is a risk of reinfection with HCV (Grebely 2011b). The second concern is the side effect profile of IFN, especially the neuropsychiatric problems that may result in a worsening of addictive behaviour (Wiegand 2006). In addition, it has been shown that the acceptance of and adherence to antiviral therapy by these patients can be low due to the side effects of IFN (Broers 2005). While a recent meta-analysis did see a difference in drug-using populations vs those not using drugs in hepatitis C treatment trials that broke out the difference (68.5% vs 81.5% SVR), the same authors went on to note that this difference may be bridged by enrolment in drug treatment or multidisciplinary treatment programs and/or requirements of abstinence from actively using drugs in order to facilitate optimal treatment outcomes (Hellard 2009).

There are open questions on the treatment of acute hepatitis C. For example, a study coordinated by the German Competence

Network for Viral Hepatitis (Hep-Net) tested if the wait-and-see strategy for 12 weeks is as effective as immediate treatment. The first preliminary data from this trial were presented at the 2009 EASL Annual Meeting. Early treatment was superior in the intent-to-treat analysis, although this was mainly due to higher drop out rates in the delayed treatment arm. Of note, all patients who started treatment later and who completed treatment and follow-up responded to treatment. The trial also showed for the first time that early treatment is as effective in patients with asymptomatic acute hepatitis C (Deterding 2009). Thus, the decision to wait for 12 weeks after diagnosis or to treat immediately may be made individually. Importantly, the compliance of the patient should be assessed. Host genetics (IL28B), other markers (IP-10), or HCV RNA kinetics during the first weeks may help to decide when to treat. For example, asymptomatic patients with IL28B rs12979860-CT or TT may be treated immediately. In the next few years we will quite possibly have new DAAs that will allow IFN-free therapies.

Patients with normal aminotransferase levels

Approximately 30% of patients with chronic hepatitis C maintain persistently normal alanine aminotransferase (ALT) levels despite having detectable HCV RNA in serum. These patients have generally mild liver disease and show a slow progression to cirrhosis. However, up to one third of patients with normal ALT can present with significant liver fibrosis necessitating an effective treatment (Bacon 2002, Zeuzem 2004a). In current guidelines, ALT elevation is not a prerequisite to start antiviral therapy and the assessment of liver disease severity should be made regardless of ALT (EASL 2011). In general, the efficacy and safety of PEG-IFN/RBV therapy in patients with persistently normal ALT levels seems to be comparable to that seen in patients with elevated ALT levels. 48 weeks of PEG-IFN α-2a plus ribavirin has been shown to lead to an SVR of 52% in patients with chronic hepatitis C and persistently normal ALT levels. Treatment-related flares in ALT activity were not observed

(Zeuzem 2004a). This has not been analysed in detail for triple therapy regimes.

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, van der Meer 2012). 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 triple therapy with HCV protease inhibitors as well (Pol 2011b) (Figure 4.7A, 4.7B). 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, Hezode 2012). In the first real-life cohorts, a platelet count <100,000-110,000 / µl was associated with serious adverse events and hospitalization (Hezode 2012, Maasoumy 2013). The rate of severe anemia requiring blood transfusions is significantly higher in patients with advanced liver cirrhosis. Some patients even experienced severe complications with fatal outcome mainly due to septicemia as a consequence of infections (Table 4.10). In general, treatment should be limited to patients with early compensated cirrhosis. In patients with advanced cirrhosis (i.e., low platelets as surrogate for portal hypertension), 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).

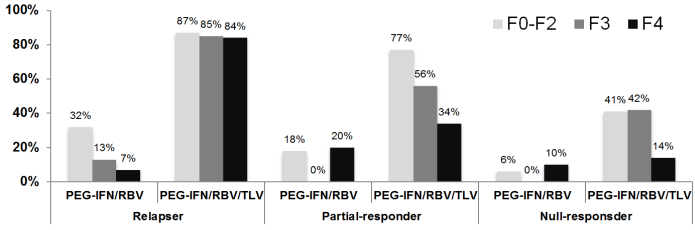

Figure 4.7A – SVR of TLV-based regimens in patients with HCV genotype 1 according to fibrosis stage. Sub-anaylsis of the REALIZE Phase III trial (Pol 2011b)

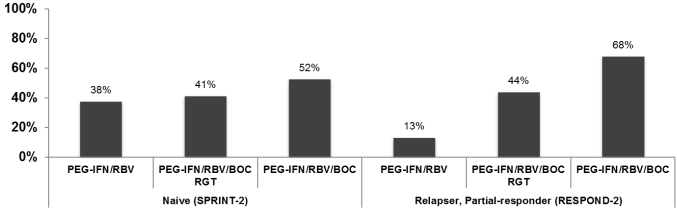

Figure 4.7B – SVR of BOC-based regimens in patients with HCV genotype 1 with advanced fibrosis and cirrhosis (F3-F4). Subanaylsis of the SPRINT-2 and RESPOND-2 trials (Bruno 2011)

Table 4.10 – Safety of triple therapy PEG-IFN/RBV and PI in patients with cirrhosis in the French real-life cohort CUPIC (Hezode 2012)

	Telaprevir (n=292)	Boceprevir (n=205)
Serious adverse events (SAE)	135 (45.2%)	67 (32.7%)
Premature discontinuation	66 (23%)	54 (26.3%)
Discontinuation due to SAEs	43 (14.7%)	15 (7.3%)
Death	5 (2.6%)	1 (0.5%)
Anemia, Grade 2 (8.0-<10.0 g/dL)	55 (18.8%)	48 (23.4%)
Anemia, Grade 3-4 (<8.0 g/dL)	34 (11.6%)	9 (4.4%)
EPO use	157 (54%)	95 (46%)
Blood transfusion	47 (16.1%)	13 (6.3%)
Neutropenia, Grade 3 (500-<1000/mm^3)	6 (2.0%)	2 (1.0%)
	2 (0.7%)	7 (3.4%)
Neutropenia, Grade 4 (<500/mm^3)	7 (2.4%)	9 (4.4%)
G-CSF use		
Thrombopenia, Grade 3 (<50,000/mm^3)	28 (9.6%)	10 (4.9%)
	2 (0.7%)	3 (1.5%)
Thrombopenia, Grade 4 (<20,000/mm^3)	4 (1.4%)	2 (1.0%)
Thrombopoietin use		
Rash, Grade 3/4	16 (5.5%)	0
Infection, Grade 3/4	19 (6.5%)	5 (2.4%)
Renal failure	5 (1.7%)	0
Hepatic decompensation	6 (2.0%)	6 (2.9%)

Patients after liver transplantation

HCV reinfection occurs in almost all patients after liver transplantation. While the course of hepatitis C in liver transplant recipients was believed to be rather benign in the late ‘80s and early ‘90s (Boker 1997), HCV has led to a more rapid progression post-transplant in recent years (Berenguer 2005, Neumann 2004) with cirrhosis within the first 5-10 years in 20-30% of patients. HCV definitely takes a more rapid course post-transplant than in immunocompetent individuals and treatment needs are obvious. Antiviral therapy of HCV may be started before transplant to prevent reinfection of the graft. If this approach is successful, reinfection can be prevented in two-thirds of patients (Forns 2003). However, treatment with

IFN/RBV is poorly tolerated in individuals with decompensated cirrhosis with a high risk for infections and this approach is feasible in only a minority of patients (Everson 2005, Forns 2003). Preemptive treatment within the first 4-6 weeks post-transplant has been disappointing with SVR between 5% and 33% for different regimens including IFN monotherapy and IFN/RBV (Terrault 2003). Studies using PEG-IFN/RBV reported an SVR of 26-48% (Carrion 2007, Dumortier 2004, Neff 2004, Roche 2008, Rodriguez-Luna 2004). Treatment duration should be at least similar to non-transplanted patients considering early viral kinetics and the HCV genotype. However, bone marrow toxicity, depression, and rejection are limiting factors that require aggressive management (e.g., growth factors) (Rodriguez-Luna 2004). The ribavirin dose may have to be adjusted since many patients have some degree of renal insufficiency. Interestingly, the risk for IFN-induced graft rejection seems to be higher if ribavirin is not used. 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). First clinical data showed some promising response data until week 12 including suggestions on how to tailor immunosuppression (Werner 2012, Coilly 2013). However, adverse events were frequent and monitoring immunosuppressive drug levels may be time-consuming and challenging. In some studies, the frequency of severe anemia was higher than 50% and mortality has also been reported (Coilly 2013). The use of PIs must be carefully evaluated after liver transplantation in relation to drug-drug interactions and tolerance. Future DAAs will change the landscape of HCV treatment especially in the setting of liver transplantation.

Hemodialysis patients

Treatment needs for dialysis patients with hepatitis C are obvious especially if patients are considered for kidney

transplantation. The outcome of HCV post-kidney transplantation is worse than for HCV-negative patients after renal transplantation. However, IFN-based therapies are contraindicated post-transplantation since they may induce rejection. Thus, if possible, HCV should be eliminated before transplantation. There have been several smaller reports on the treatment of HCV with IFN monotherapy in patients with end-stage renal disease (Fabrizi 2002). Surprisingly, the results for IFN monotherapy on dialysis were better than in patients not undergoing dialysis, with SVR results of 21-64%. Data on combination with ribavirin are limited since ribavirin is contraindicated in this setting. However, ribavirin can be given at lower doses in dialysis patients, usually at 200-400 mg daily (Bruchfeld 2001). It has to be considered that there may be significant differences between the two pegylated interferons in the setting of dialysis since PEG-IFN α-2a is eliminated mainly by the liver while PEG-IFN α-2b is cleared via the kidney (reviewed in Cornberg 2002). Thus, only PEG-IFN α-2a should be used in this setting. The efficacy of BOC and TLV has not been tested in HCV patients with end stage renal disease or in patients undergoing hemodialysis. Theoretically, BOC and TLV can be administered in patients with compensated renal insufficiency and dose adjustment is not necessary because both drugs are metabolized through the liver and mainly eliminated via the feces with minimal urinary excretion (Ghany 2011).

Drug abuse and patients on stable maintenance substitution

Treatment of patients with active drug use is an individual approach and should only be performed in an experienced multidisciplinary setting including hepatologists, psychiatrists and addictologists. Drug interactions with BOC and TLV need to be considered.

Patients with coinfections

Due to the similar routes of transmission, patients with chronic hepatitis C are frequently coinfected with hepatitis B virus,

hepatitis D virus or human immunodeficiency virus. This important patient group is discussed in more detail in Hepatology Textbook, Chapters 10, 17 and 18.

Patients with hemophilia

Due to contaminated clotting factor concentrates many patients with hemophilia are infected with HCV and/or HIV. Studies investigating PEG-IFN/RBV in hemophilia patients are limited and often include small numbers of patients. Review of available data suggest that treatment success of HCV-infected hemophiliacs is similar to that achieved in the general HCV-infected population (Franchini 2008).

Patients with extrahepatic manifestations

More than 50% of HCV-infected patients suffer from extrahepatic manifestations ranging from fatigue to severe symptoms of mixed cryoglobulinemia (Cacoub 1999) (see Hepatology Textbook, Chapter 15). The primary goal of treatment is HCV eradication, which is associated with improvement of clinical symptoms, especially in patients with mixed cryoglobulinemia (Cresta 1999, Pischke 2008, Zignego 2007). Insulin resistance can be improved in HCV GT1 patients with SVR (Thompson 2012). In patients with severe symptoms of mixed cryoglobulinemia, treatment with rituximab may be considered (Cacoub 2008). Recent studies have also tested the combination of PEG-IFN/RBV and rituximab. The clinical response may be achieved faster and SVR is not diminished in patients who receive rituximab (Dammacco 2010, Saadoun 2010). Exacerbation of certain extrahepatic manifestations may occur with IFN-based therapy or IFN may be contraindicated (Zignego 2007). The first studies using HCV PIs have been started in patients with HCV and mixed cryoglobulinemia vasculitis. After 3 months, triple therapy was highly effective in terms of virological response as well as clinical response, but adverse events were frequent (>80% anemia, >50% infections) (Saadoun 2012). Similar to patients after transplantation, a PI regimen

should be administered cautiously considering the high rates of side effects.

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 response in only a few patients. In 2013, treatment is successful in up to 80% of a broader selection of patients. Many issues remain to be addressed, though. Treatment is costly and not readily available for patients in many areas where hepatitis C prevalence is high. Treatment is not easy, either. It often lasts 6 to 12 months and the drugs are not always well tolerated.

Further progress is looming. Knowledge of the molecular structure of the hepatitis C proteins has allowed the design of new drugs targeting the sites of many HCV-encoded enzymes that are important for the replication of the virus. Approval of the first protease inhibitors came in 2011. Even if PEG-IFN and ribavirin remain the backbone of standard therapy in the short term, the new oral drugs, eventually comprising complete oral regimens, may be able to transform chronic hepatitis C infection into a curable disease for a majority of patients. Further improvements may be "just around the corner".

5. Hepatitis C: New Drugs

Christian Lange, Christoph Sarrazin

Introduction

Combination therapy with pegylated interferon α plus weight-based ribavirin leads to sustained virologic response (SVR, defined by undetectable HCV RNA 24 weeks after treatment completion) in approximately 50% of all HCV genotype 1-infected patients, compared to 70-90% of those infected with HCV genotypes 2 and 3 (Zeuzem 2009). The limited treatment success especially in HCV genotype 1 patients, the need for long treatments (up to 72 weeks), the numerous side effects of PEG-IFN α plus ribavirin therapy, and the exploding knowledge of the HCV life cycle and of structural features of the HCV proteins has spurred development of many promising directly acting antiviral agents (DAA) (Bartenschlager 2004, Lange 2012, Moradpour 2007).

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) and host targeting agents (HTAs) in the pipeline

Drug name	Company	Target / Active site	Phase
NS3/4A protease inhibitors			
Telaprevir (VX-950)	Vertex	Active site / linear	IV
Boceprevir (SCH503034)	Merck	Active site / linear	IV
Simeprevir (TMC435)	Janssen / Medivir	Active site / macrocyclic	III
Danoprevir (R7227)	Roche / InterMune	Active site / macrocyclic	III
Vaniprevir (MK-7009)	Merck	Active site / macrocyclic	III
MK-5172	Merck	Active site / macrocyclic	II
Faldaprevir (BI201335)	Boehringer Ingelheim	Active site / linear	III
Asunaprevir (BMS-650032)	Bristol-Myers Squibb	Active site	II
GS-9256	Gilead	Active site	II
GS-9451	Gilead	Active site	II
ABT-450	Abbott	Active site	III
IDX320	Idenix	Active site	II
ACH-1625	Achillion	Active site / macrocyclic?	II
Nucleoside analog NS5B polymerase inhibitors (NI)			
Mericitabine (R7128)	Roche / Pharmasset	Active site	III
Sofosbuvir (GS-7977)	Gilead	Active site	III
ALS-220	Alios / Vertex	Active site	II
Non-nucleoside NS5B polymerase inhibitors (NNI)			
BI207127	Boehringer Ingelheim	NNI site 1 / thumb 1	II
BMS-791325	Bristol-Myers Squibb	NNI site 1 / thumb 1	II
TMC647055	Janssen	NNI site 1 / thumb 1	I
Filibuvir (PF-00868554)	Pfizer	NNI site 2 / thumb 2	II
VX-222	Vertex	NNI site 2 / thumb 2	II
GS-9669	Gilead	NNI site 3 / palm 1	II
ABT-333	Abbott	NNI site 3 / palm 1	II
Tegobuvir (GS-9190)	Gilead	NNI site 4 / palm 2	II
Setrobuvir (ANA598)	Anadys	NNI site 4? / palm 1	II
NS5A inhibitor			
Daclatasvir (BMS-790052)	Bristol-Myers Squibb	NS5A domain 1 inhibitor	III
BMS-824393	Bristol-Myers Squibb	NS5A protein	I
PPI-461	Presidio	NS5A protein	I
GS-5885	Gilead	NS5A protein	II
ABT-267	Abbott	NS5A protein	II
ACH-2928	Achillion	NS5A protein	I
MK-8742	Merck	NS5A protein	I
Host targeting agents			
SCY-635	Scynexis	Cyclophilin inhibitor	II
Miravirsen	Santaris	miRNA122 antisense RNA	II

Table 5.1a – Selected directly acting antiviral agents (DAAs) and host targeting agents whose development has recently been stopped or temporarily halted

Drug name	Company	Target / Active site
NS3/4A protease inhibitors		
Ciluprevir (BILN 2061)	Boehringer Ingelheim	Active site / macrocyclic
Narlaprevir (SCH900518)	Schering-Plough	Active site / linear
PHX1766	Pheromix	Active site
Nucleoside analog NS5B polymerase inhibitors (NI)		
Valopicitabine (NM283)	Idenix/ Novartis	Active site
R1626	Roche	Active site
GS-938	Gilead	Active site
IDX184	Idenix	Active site
Non-nucleoside NS5B polymerase inhibitors (NNI)		
BILB 1941	Boehringer Ingelheim	NNI site 1 / thumb 1
MK-3281	Merck	NNI site 1 / thumb 1
VX-759	Vertex	NNI site 2 / thumb 2
VX-916	Vertex	NNI site 2 / thumb 2
ABT-072	Abbott	NNI site 3 / palm 1
HCV-796	ViroPharma / Wyeth	NNI site 4 / palm 2
IDX375	Idenix	NNI site 4 / palm 2
Host targeting agents		
Alisporivir (Debio-025)	Novartis	Cyclophilin inhibitor
NIM811	Novartis	Cyclophilin inhibitor

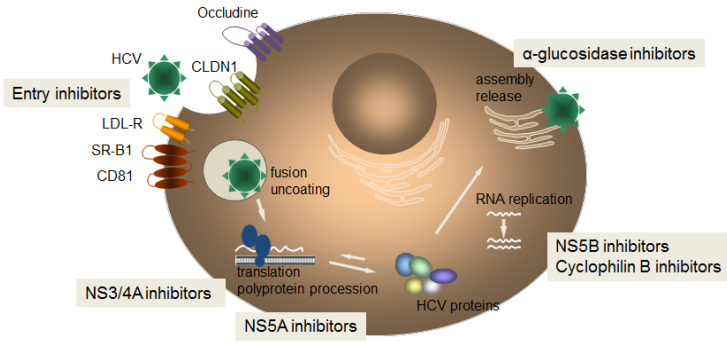

Figure 5.1 – HCV life cycle and targets for directly acting antiviral (DAA) agents

Recently, the NS3/4A protease inhibitors telaprevir and boceprevir were approved in combination with PEG-IFN α plus ribavirin (triple therapy). However, escpecially for patients with previous failure to PEG-IFN α / RBV therapy, efficacy of triple therapy with telaprevir or boceprevir is limited and a large proportion of patients continue to be intolerant to the side effects associated with IFN α. The current development of novel interferon-free DAA combination regimens is eagerly awaited.

HCV life cycle and treatment targets

HCV is a positive-sense single-stranded RNA virus of approximately 9600 nucleotides. The HCV genome contains a single large open reading frame encoding for a polyprotein of about 3100 amino acids. From this initially translated polyprotein, the structural HCV protein core (C) and envelope glycoproteins 1 and 2 (E1, E2), p7, and the six non-structural HCV proteins NS2, NS3, NS4A, NS4B, NS5A and NS5B, are processed by both viral and host proteases. The core protein forms the viral nucleocapsid carrying E1 and E2, the receptors for viral attachment and host cell entry. The non-structural proteins are multifunctional proteins essential for the HCV life cycle (Bartenschlager 2004, Moradpour 2007). P7 is a small hydrophobic protein that oligomerizes into a circular hexamer, most likely serving as an ion channel through the viral lipid membrane. The large translated section of the HCV genome is flanked by the strongly conserved HCV 3' and 5' untranslated regions (UTR). The 5' UTR is comprised of four highly structured domains forming the internal ribosome entry site (IRES), which plays an important role in HCV replication (Figure 5.2).

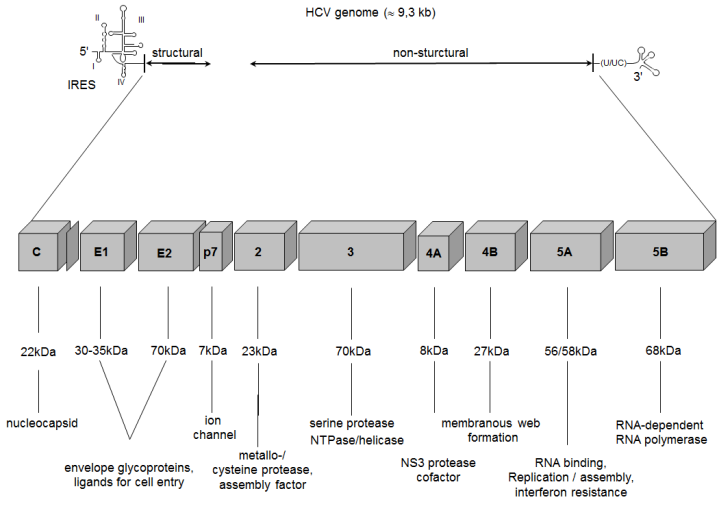

Figure 5.2 – Genomic organisation of HCV

NS3/4A protease inhibitors

Molecular biology

After receptor-mediated endocytosis, the fusion of HCV with cellular membranes and 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) (Bartenschlager 2004, Moradpour 2007). IRES mediates the 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 (Bartenschlager 2004, 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), which activates the serine protease, located in a small groove, and the helicase/NTPase (Kim 1998, Kim 1996). NS3 forms a tight, non-covalent complex with its cofactor and enhancer NS4A, which is essential for proper protein folding (Figure 5.3). 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 may play an important role in HCV persistence via blocking TRIF-mediated toll-like receptor signaling and Cardif-mediated RIG-I signaling, 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.

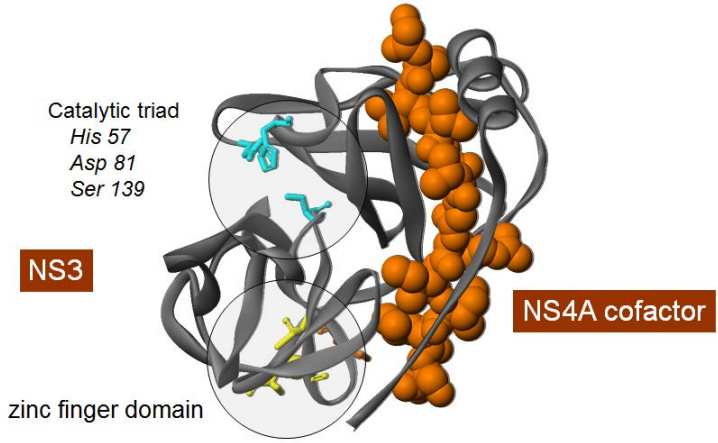

Figure 5.3 – Molecular structure of the HCV NS3/4A protease

The location of the active site of the NS3/4A protease, the shallow groove mentioned previously, makes the design of compound inhibitors relatively difficult. Nevertheless, many

NS3/4A protease inhibitors have been developed which can be divided into two classes, the macrocyclic inhibitors and the linear tetrapeptide-based α-ketoamide derivatives. In general, NS3/4A protease inhibitors have been shown to strongly inhibit HCV replication during monotherapy but can also cause the selection of resistant mutants followed by viral breakthrough. The additional administration of pegylated interferon plus ribavirin, however, was shown to reduce the frequency of development of resistance. The logical aim for combination therapies with different antiviral drugs is to be efficacious while preventing the development of resistance.

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

Telaprevir and boceprevir were approved for the treatment of chronic hepatitis C virus genotype 1 infection by 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-ketoamide derivatives (Figure 5.4).

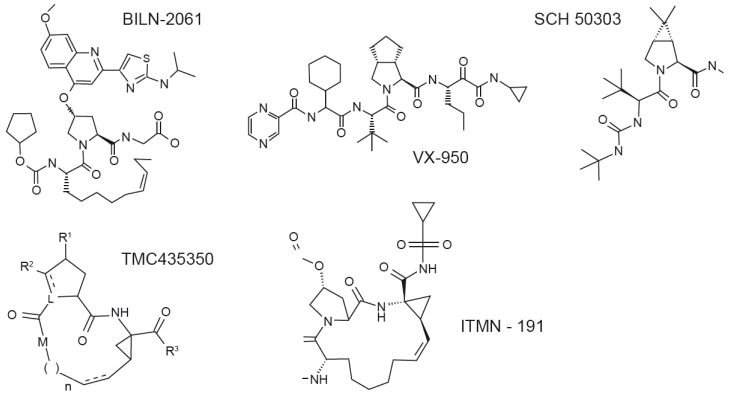

Figure 5.4 – Molecular structure of selected NS3/4A inhibitors

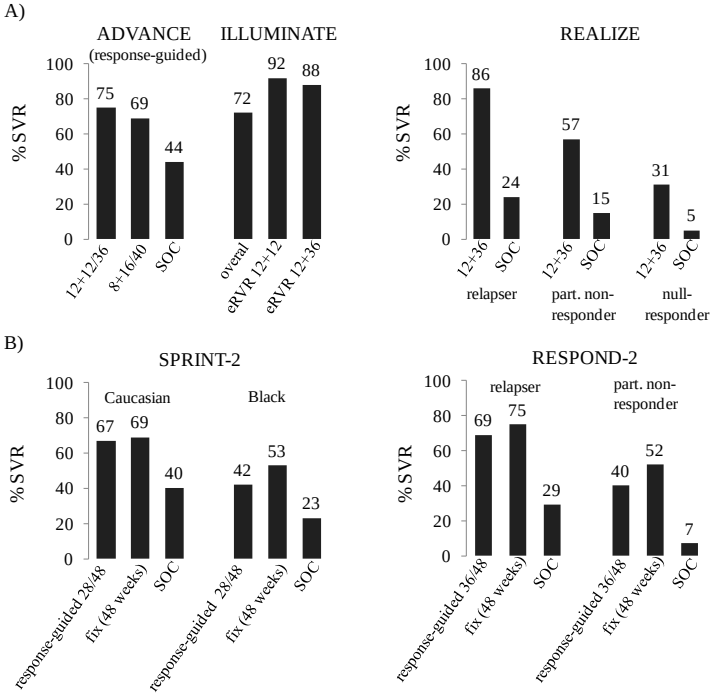

Figure 5.5 – SVR rates in Phase III clinical trials evaluating telaprevir (A) or boceprevir (B) in combination with PEG-IFN α plus ribavirin (RBV). ADVANCE, ILLUMINATE and SPRINT-2 enrolled treatment-naïve patients, REALIZE and RESPOND-2 enrolled treatment-experienced patients. Telaprevir was administered for 8 or 12 weeks in combination with PEG-IFN α-2a plus RBV, followed by 12-40 weeks of PEG-IFN α-2a plus RBV alone. Boceprevir was administered over the whole treatment period of 28 or 48 weeks in combination with PEG-INF α-2b plus RBV, except for the first 4 weeks of lead-in therapy of PEG-IFN α-2b plus RBV only. eRVR, extended early virologic response; SOC, standard of care; LI, lead-in (4 wks of PEG-INF α plus RBV only)

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 studies showed 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 PEG-IFN plus RBV alone (reviewed in Lange 2012). Telaprevir- and boceprevir-based triple therapies form the new standard of care for HCV genotype 1 patients. Results of the Phase III telaprevir and boceprevir registration studies are summarized in Figure 5.5. Futher details on telaprevir- and boceprevir-based triple therapies are discussed in Chapters 4 and 6.

Other NS3 protease inhibitors

Other NS3 protease inhibitors are currently in various stages of development - danoprevir (R7227), faldaprevir (BI201335), simeprevir (TMC435), asunaprevir (BMS-650032), ACH-1625, IDX320, ABT-450, MK-5172, GS-9256, GS-9451 - and should 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, Dvory-Sobol 2012, Lawitz 2012, Manns 2011, Manns 2011, Reesink 2010, Summa 2012). Potential advantages of these second and third generation protease inhibitors may be improved tolerability, broader genotypic activity (e.g., MK-5172, danoprevir, simeprevir), different resistance profiles (e.g., MK-5172), and/or improved pharmacokinetics for once-daily dosing (e.g., simeprevir, faldaprevir). Different resistance profiles between linear tetrapeptide and macrocyclic inhibitors binding to the active site of the NS3 protease have been shown. R155 is the main resistance codon and different mutations at this amino acid site within the NS3 protease confer cross-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 (Romano 2012). MK-5172 also shows potent antiviral activity against HCV genotypes 1 and 3 isolates, although the required doses to suppress HCV gentoype 3 may be too high due to toxicity issues (Brainard 2010).

The currently most advanced NS3/4A protease inhibitors are faldaprevir and simeprevir (Phase III, January 2013). In Phase II clinical trials, simeprevir 150 mg once daily for 12-24 weeks in combination with PEG-IFN α / RBV for 24-48 weeks was well tolerated and resulted in overall SVR rates of 81-86% in treatment-naïve HCV genotype 1 patients (PILLAR study) and of 67-80% in treatment-experienced HCV genotype 1 patients (ASPIRE study) (Fried 2012). Somewhat lower SVR rates were observed for faldaprevir-based triple therapy in Phase II clinical trials. In SILEN-C1, SILEN-C2, and SILEN-C3, treatment with faldaprevir (120-240 mg once daily) for 12-24 weeks in combination with PEG-IFN α / RBV for 24-48 weeks resulted in overall SVR rates of 65-83% in treatment-naïve HCV genotype 1 patients and of 27-41% in treatment-experienced HCV genotype 1 patients (Dieterich 2011, Sulkowski 2011, Sulkowski 2011). The approval of faldaprevir and simeprevir is expected for 2014/2015.

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, Sarrazin 2010). 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 pre-existing 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 plus 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. Although the resistance profiles differ significantly, R155 is an overlapping position for resistance development and different mutations at this position confer resistance to nearly all protease inhibitors (although not MK-5172) currently in advanced clinical development (Sarrazin 2010). 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 the 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).

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 plus RBV, 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). In addition, HCV genotype 1a isolates generally display a higher fitness compared to HCV genotype 1b isolates, which explains a higher risk of resistance development at other positions within NS3/4A and other genomic regions of HCV genotype 1a (Romano 2012).

It will be important to better define whether treatment failure due to the development of variants resistant to DAA agents has a negative impact upon re-treatment with the same or different DAA treatment regimens. 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) using 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). Furthermore, re-treatment with simeprevir-based triple therapy in 5 patients who had developed simeprevir resistance previously during monotherapy resulted in SVR in only 3 out of 5 patients, indicating a possible effect of low-level persistence of resistant variants (Lenz 2012).

Table 5.2 – Resistance mutations to selected HCV NS3 protease inhibitors

	36	54	55	80	155	156A	156B	168	170
Telaprevir* (linear)	■	■			■	■	■		
Boceprevir* (linear)	■	■	■		■	■			■
SCH900518* (linear)	■	■			■	■	■		■
BI201335* (linear)					■			■	
BILN 2061** (macrocyclic)					▒		▒	▒	
Danoprevir* (macrocyclic)					▒			▒	
MK-7009* (macrocyclic)					▒		▒	▒	
TMC435* (macrocyclic)				▒	▒		▒	▒	
BMS-650032* (macrocyclic)				▒	▒			▒	
GS-9451* (macrocyclic)					▒			▒	
ABT-450* (macrocyclic)					▒			▒	
IDX320** (macrocyclic)								▒	
ACH-1625** (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 on 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

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 5.6). 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. Due to the lack of proofreading of the NS5B polymerase together with the high replication rate of HCV, every possible mutation is generated every day.

NS5B RNA polymerase inhibitors can be divided into two distinct categories. Nucleoside analog inhibitors (NIs) like mericitabine, sofosbuvir, or ALS-220 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 the development of resistance 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 5.6). Because of their distinct binding sites, different NNI (polymerase) inhibitors can theoretically be used in combination or in sequence to manage the development of resistance.

But because NNIs bind relatively distantly from the active center of NS5B (see Figure 5.7), 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 5.7 shows the structure of selected nucleoside and non-nucleoside inhibitors as well as the active center.

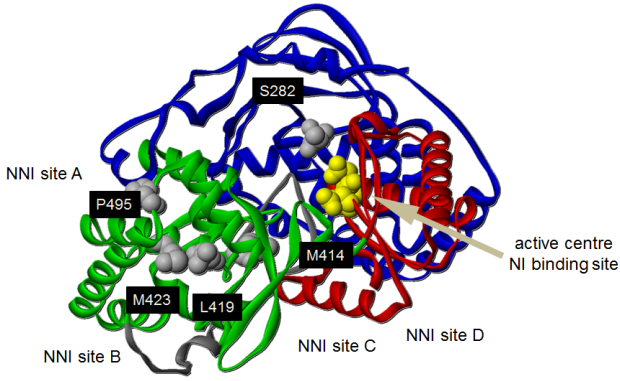

Figure 5.6. Structure of the HCV NS5B RNA polymerase and binding sites

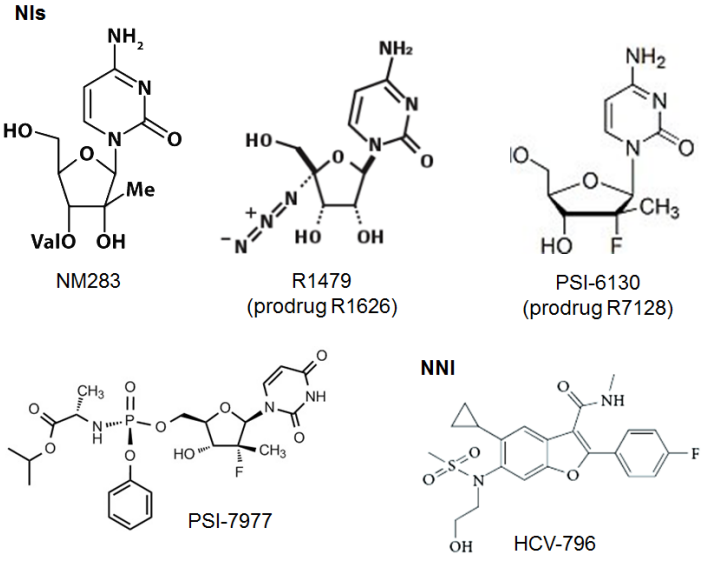

Figure 5.7 – Molecular structure of selected NS5B polymerase inhibitors

Nucleoside analogs

Mericitabine (RG7128) is safe and well-tolerated, moderately effective against all HCV genotypes, and thus far viral resistance against mericitabine has been observed very rarely in clinical studies. Mericitabine-based triple therapies in HCV genotype 1-, 2-, 3-infected patients revealed superior SVR rates compared to PEG-IFN α alone (Pockros 2011). In an all-oral regimen, administration of mericitabine in combination with the protease inhibitor R7227 (danoprevir) 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.

Very promising clinical data have been published recently for sofosbuvir, a nucleoside analog NS5B inhibitor effective against all HCV genotypes. In HCV genotype 1-, 2-, and 3-infected patients, short durations of sofosbuvir (400 mg once daily) in combination with PEG-IFN α plus RBV resulted in 90-100% SVR rates (Gane 2013, Gane 2011, Lawitz 2011). No sofosbuvir-associated side effects have been reported, and no virologic breakthrough has been observed during triple therapy. Furthermore, some very promising sofosbuvir-based interferon-free regimens are under development (see below). Thus far, sofosbuvir resistance has only been observed in single patients after sofosbuvir monotherapy (mutation S282T) (Svaroyskaia 2012).

Overall, nucleoside analogs like sofosbuvir 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 (e.g., thumb 1 inhibitors BI207127, BMS-791325; thumb 2 inhibitors filibuvir and VX-222; palm I inhibitor ANA598 and ABT-333; palm II inhibitors tegobuvir and IDX-375) (Ali 2008, Cooper 2007, Erhardt 2009, Kneteman 2009, Larrey 2012). 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 during 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 in combination with pegylated interferon plus RBV 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 PEG-IFN plus RBV therapy (except as components of quadruple therapy) 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 was 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).

Daclatasvir (BMS-790052) was the first NS5A inhibitor to be clinically evaluated. Even low doses of daclatasvir display high antiviral efficacy against all HCV genotypes *in vitro*. Monotherapy with daclatasvir led to a sharp initial decline of HCV RNA concentrations, though its genetic barrier to resistance is relatively low (Gao 2010). In HCV genotype 1 and 4 patients, daclatasvir-based triple therapies for 24 or 28 weeks led to extended RVR (eRVR) rates of up to 83% of patients, compared to 9% in the control group (Pol 2012). SVR rates in this study ranged from 59-100%, according to daclatasvir dosage and HCV genotype / subtype (Hezode 2012).

During monotherapy, rapid selection of variants resistant to daclatasvir 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 daclatasvir moderately to strongly (Fridell 2011). However, no cross-resistance between daclatasvir and other DAA agents has been reported. Collectively, daclatasvir 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, ABT-267) are in clinical development. Like daclatasvir, these NS5A inhibitors are characterised by broad genotypic coverage, high antiviral activity, but also by a low genetic barrier to resistance development and overlapping resistance profiles (cross-resistance).

Compounds targeting viral attachment and entry

The tetraspanin protein CD81, claudin-1, occludine, scavenger receptor class B type 1 (SR-B1), the low-density lipoprotein (LDL) receptor, glycosaminoglycans and the dendritic cell- /lymph node-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN/L-SIGN) have been identified as putative ligands for E1 and E2 during viral attachment and entry (Moradpour 2007).

HCV entry inhibition might enrich future hepatitis C treatment opportunities, in particular in the prevention of HCV liver graft reinfection. HCV entry inhibition can be theoretically achieved by the use of specific antibodies or small molecule compounds either blocking E1 and E2 or their cellular receptors. So far, only results from clinical trials using polyclonal (e.g., civacir) (Davis 2005) or monoclonal (e.g., HCV-AB 68) (Schiano 2006) HCV-specific antibodies are available. The clinical benefit

of these antibodies has been poor, however. The development of small molecule entry inhibitors is in a preclinical stage and is complicated by difficulties in the crystallographic characterization of the HCV envelope proteins.

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. Alisporivir (Debio-025) 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 alisporivir 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). Alisporivir was well-tolerated and no viral breakthrough occurred during the 14 days of treatment.

Combination therapy of alisporivir 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 alisporivir alone) in the monotherapy groups. No differences in antiviral activity were observed between individuals infected with the different genotypes. Alisporivir was safe and well tolerated but led to a reversible bilirubin increase in some of the patients treated with 1000 mg alisporivir daily (Flisiak 2009). A high genetic barrier to

resistance of alisporivir 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 alisporivir, PEG-IFN α-2a plus ribavirin for 24-48 weeks resulted in SVR rates of 69-76% compared to 55% in the control group (Flisiak 2011). Furthermore, interesting first studies with interferon-free treatment regimens including alisporivir and ribavirin have been conducted. Despite these promising data, the development of alisporivir is currently on hold due to rare cases of severe pancreatitis during combination therapy with alisporivir and PEG-IFN α-2a.

Nitazoxanide

Nitazoxanide with its active metabolite tizoxanide is a thiazolide antiprotozoal approved for the treatment of *Giardia lamblia* and *Cryptosporidium parvum* infections. *In vitro* studies have revealed an essential inhibitory impact on HCV and HBV replication by still unknown mechanisms.

Results of two Phase II studies evaluating 500 mg nitazoxanide twice daily for 12 weeks followed by nitazoxanide, PEG-IFN α-2a ± RBV for 36 weeks yielded conflicting results with SVR rates of 79% in treatment-naïve genotype 4 patients, but of only 44% in HCV genotype 1 patients (Rossignol 2009). However, additional studies revealed a less impressive gain in SVR rates with the addition of nitazoxanide to PEG-IFN α-2a plus RBV.

Silibinin

Silymarin, an extract of milk thistle (*Silybum marianum*) with antioxidant activity, has been empirically 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 after 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 to 4.85 $\log_{10}$ IU/ml (Ferenci 2008). On a case report basis, it was shown that treatment with silibinin can prevent recurrent hepatitis C after liver transplantation in selected cases (Neumann 2010).

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 previous partial or null response to treatment with PEG-IFN α plus ribavirin, in patients with limited HCV viral load decline during lead-in treatment with PEG-IFN α plus ribavirin only, 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, triple therapy regimens including more potent DAAs, or quadruple therapies based on the combination of two different DAAs plus PEG-IFN α / ribavirin may be applicable. Several triple therapy regimens including newer NS3/4A, NS5A, or NI NS5B inhibitors have been shown to be possibly superior over telaprevir or boceprevir-based triple therapy (Feld 2012, Gane 2013, Lenz 2012). Furthermore, a high potential of the quadruple therapy approach has already been demonstrated in Phase I and II clinical trials, with outstanding SVR rates even in previous null responders to PEG-IFN α plus ribavirin alone. However, these clinical trials were performed in highly selected patients, and both triple and quadruple therapy approaches are not an option for patients with contraindications to PEG-IFN α or ribavirin, such as patients with decompensated liver cirrhosis or liver transplant failure.

For that reason, numerous trials have been initiated to investigate the potential of interferon-free combination therapies with different DAA agents (+/- ribavirin) alone (Table 5.3). As is well established in the treatment of HIV infection, combining 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 combinations (Sarrazin 2010).

Table 5.3 – Selected trials evaluating DAA combination therapies

DAAs	Additional agents	Phase
Nucleoside NS5B inhibitor		
Sofosbuvir	+ / - ribavirin, + / - PEG-IFN α plus RBV	III
Nucleoside NS5B inhibitor + NS3/4A protease inhibitor		
Mericitabine + danoprevir/ritonavir	+ / - ribavirin, + / - PEG-IFN α plus RBV	III
Nucleoside NS5B inhibitor + NS5A inhibitor		
Sofosbuvir + daclatasvir	+ / - ribavirin	II
Sofosbuvir + GS-5885	+ / - ribavirin	II
Non-nucleoside NS5B inhibitor + NS3/4A protease inhibitor		
Faldaprevir + BI201335	+ ribavirin, + / - PEG-IFN α plus RBV	III
Tegobuvir + GS-9256	+ / - ribavirin, + / - PEG-IFN α plus RBV	II
ABT-333 + ABT-450/r	+ ribavirin + / - PEG-IFN α	III
ABT-072 + ABT-450/r	+ ribavirin	II
VX-222 + telaprevir	+ / - ribavirin, + / - PEG-IFN α plus RBV	III
NS3/4A protease inhibitor + NS5A inhibitor		
Asunaprevir + daclatasvir	+ / - ribavirin, + / - PEG-IFN α plus RBV	III
Multiple DAA agent combinations		
NS5A inhibitor (GS-5885) + NS3/4A inhibitor (GS-9451) + NNI (tegobuvir)	+ ribavirin	II
NS5A inhibitor (ABT-267) + NS3/4A inhibitor (ABT-450/r) + NNI (ABT-333)	+ ribavirin	II
NS5A inhibitor (daclatasvir) + NS3/4A inhibitor (asunaprevir) + NNI (BMS-791325)	-	II
Host targeting agents		
Alisporivir	+ / - ribavirin, + / - PEG-IFN α plus RBV	Halted

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. Despite

their low antiviral efficacy and low genetic barrier to resistance development, some NNI NS5B inhibitors have been shown to be valuable partners in all-oral regimens.

In the following section, current data on combination therapies of different DAAs, with or without PEG-IFN α and / or RBV will be summarized.

PEG-IFN α-based quadruple therapy

Preliminary SVR data of a small but highly informative trial serves as proof-of-concept for the potential of a quadruple therapy approach for patients with previous null response to PEG-IFN α plus RBV (Lok 2012). In one Phase II study, 11 HCV genotype 1 patients with prior null response were treated with a combination of the NS5A inhibitor daclatasvir and the protease inhibitor asunaprevir together with PEG-IFN α plus 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, the high SVR rate seems impressive compared to SVR rates of ~30% that were achieved with telaprevir-based triple therapy in prior null responders (Zeuzem 2011). The efficacy of this quadruple regimen in both HCV genotype 1a and 1b patients with prior null response has since been confirmed in a larger trial (Lok 2012).

A Phase II clinical trial assessed quadruple therapy with the non-nucleoside NS5B inhibitor tegobuvir in combination with the NS3/4A protease inhibitor GS-9256 + PEG-IFN α plus RBV 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.

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 plus RBV 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 plus ribavirin alone. Up to 50% of patients met the criteria for the 12-week treatment. Of those, 82-93% achieved an SVR 12 weeks after treatment. In patients who were treated with an additional 12 weeks of PEG-IFN α plus RBV, the end-of-treatment response was 100%.

Recently, a head-to-head comparision of triple-therapy, quadruple therapy, and interferon-free therapy based on the NI mericitabine was reported (Matterhorn trial) (Feld 2012). In this study, HCV gentoype 1a and 1b patients with prior partial- or null-response were randomized to treatment with either mericitabine plus PEG-IFN α / RBV (triple therapy), mericitabine in combination with the NS3/4A protease inhibitor danoprevir/ritonavir plus PEG-IFN α / RBV (quadruple therapy), or mericitabine in combination with danoprevir/ritonavir and ribavirin (interferon-free). According to an incomplete preliminary analysis, SVR rates were 95%, 100%, and 44-72% in the triple-, quadruple, and interferon-free treatment arm, respectively. HCV gentoype 1a patients in particular experienced high rates of viral breakthrough on the interferon-free therapy. Importantly, viral breakthrough was associated with resistance to danoprevir but not to mericitabine. Collectively, the quadruple therapy approach appears to be highly promising in patients with limited sensitivity to IFN α, even in patients with HCV subtype 1a and prior null response to PEG-IFN α / RBV.

All-oral therapy with or without ribavirin

Combinations of NS3/4A protease inhibitors and nucleoside analog NS5B inhibitors, with or without ribavirin

A first interferon-free clinical trial (INFORM-1 study) evaluated the combination of the NI mericitabine with the NS3/4A

inhibitor danoprevir. In this proof of concept study, patients received both compounds for up to 14 days (Gane 2010). HCV RNA declined up to 5.2 $\log_{10}$ IU/ml, viral breakthrough occurred in a single patient, and HCV RNA was undetectable at the end of dosing in up to 63% of patients. However, the fundamental question of whether an SVR can be achieved with combination therapies of different DAA compounds without PEG-IFN α plus RBV had to be answered by subsequent trials.

In the meantime, the INFORM-SVR study provided SVR data for the combination of mericitabine and danoprevir/r (ritonavir-boosted) with or without ribavirin for 12-24 weeks (Gane 2012). SVR rates in HCV genotype 1a and 1b patients were 26% and 71% in treatment arms including ribavirin (n=83), respectively, but significantly lower in all the RBV-free treatment groups (n=86). Importantly, resistance-associated variants in patients with viral breakthrough were predominantly identified within NS3/4A while a resistance mutation in NS5B was discovered only in one single patient (S282T). Recently, the large Matterhorn trial has shown in a head-to-head comparision that, in prior partial and null responders, IFN-free therapy containing mericitabine, danoprevir and ribavirin generally resulted in lower SVR rates than danoprevir-based triple therapy or quadruple therapy, especially in patients with HCV genotype 1a (Feld 2012).

Promising Phase II clinical trials assessed the combination of the NI sofosbuvir (GS-7977) +/- RBV. In QUANTUM, treatment-naïve HCV genotype 1, 2 and 3 patients were treated for 12-24 weeks with sofosbuvir plus ribavirin. Of those HCV genotype 1 patients who completed the 12-week course of therapy, 59% achieved SVR at week 4 post-treatment (Gilead press release 2012). In ELECTRON, the same 12-week regimen resulted in SVR in only 11% (1/9) of HCV genotype 1a null responders, but in 88% (22/25) of treatment-naïve HCV genotype 1 patients. In treatment-naïve and treatment experienced HCV genotype 2 and 3 patients, SVR rates were 100% (10/10) and 80% (12/15), respectively (Gane 2013, Gane 2012). The ELECTRON study also evaluated sofosbuvir monotherapy in treatment-naïve HCV

genotype 2 and 3 patients, which resulted in SVR in only 60% (6/10) of patients, highlighting again the important role of ribavirin in interferon-free treatment regimens (Gane 2013). Furthermore, it was shown that reduction of ribavirin dosage and shorter treatment durations than 12 weeks may negatively impact treatment outcome even in treatment-naïve HCV gentoype 2 and 3 patients (Gane 2012). Hence, therapy with sofosbuvir plus ribavirin for 12 weeks appears to be a potent and highly promising regimen for treatment-naïve HCV genotype 2 and 3 patients. In patients with HCV genotype 1 infection, or in HCV genotype 2 and 3 patients with unfavourable baseline characteristics, longer treatment durations of sofosbuvir plus ribavirin therapy may have improved efficacy. Another highly promising approach might be the addition of a second DAA, after Gilead's announcement of a 100% SVR rate in HCV gentoype 1 patients treated with sofosbuvir, RBV plus the NS5A inhibitor GS-5885 (Gilead press release 2012).

Phase III approval trials (FISSION, POSITRON, FUSION, and NEUTRINO) have since been initiated to evaluate sofosbuvir + ribavirin for 12-16 weeks in HCV genotype 2 and 3 patients.

Combinations of NS3/4A protease inhibitors and non-nucleoside analog NS5B inhibitors, with or without ribavirin

The SOUND-C1 trial assessed the combination of the NS3/4A inhibitor BI201335, the NNI BI207127 (400 or 600 mg q8h) and ribavirin for 4 weeks (Zeuzem 2011). Virologic response rates in patients treated with 600 mg q8h of BI207127 were 82%, 100% and 100% at treatment days 15, 22, and 29, respectively (SVR rates for this regimen were not provided). Overall virologic response rates were lower in subtype 1a vs. subtype 1b patients. Importantly, the large SOUND-C2 trial provided SVR rates for BI201335 in combination with BI207127 with or without RBV, administered for 16-40 weeks in approximately 360 treatment-naïve HCV genotype 1 patients (Zeuzem 2012). Overall, SVR12 rates ranged from 56% to 68% in treatment arms including ribavirin, compared to 39% in a single RBV-free treatment arm.

In all treatment arms, SVR rates were consistently higher in HCV genotype 1b than in 1a patients, or in patients with the "good response" IL28B genotype. Importantly, SOUND-C2 included a significant number of patients with liver cirrhosis. In these patients, SVR rates were promising, though lower than in patients without advanced liver disease (Soriano 2012). In SOUND-C2, the predominantly observed resistance-associated variants in patients with virologic failure were at position R155 in NS3 and at position P495 in NS5B, including double mutations in numerous patients, especially those with on-treatment failure (Cote-Martin 2012).

The combination of tegobuvir (GS-9190), another NNI, together with GS-9256, a NS3/4A inhibitor, +/- ribavirin was assessed in a trial of treatment-naïve HCV genotype 1 patients (Zeuzem 2011). Again, tegobuvir + GS-9256 + ribavirin led to higher RVR rates compared to tegobuvir + GS-9256 alone (38% versus 7%, respectively), further proving the benefit of ribavirin in distinct interferon-free DAA combination therapies.

A comparable approach is followed in the ZENITH trial, assessing the antiviral activity of the NS3/4A inhibitor telaprevir and the NNI VX-222 alone, in combination with RBV, or in combination with PEG-IFN α plus ribavirin (quadruple therapy) in treatment-naïve HCV genotype 1 patients. Again, quadruple therapy led to high SVR rates. However, in the all-oral treatment arms, high rates of viral breakthrough were observed (Jacobson 2012, Nelson 2011).

The above described data for all-oral combinations based on NS3/4A inhibitors plus NNIs are contrasted by strongly encouraging results of the recent Co-Pilot study. In Co-Pilot, 12 weeks of combination therapy with the NS3/4A inhibitor ABT-450/r (ritonavir-boosted), the NNI ABT-333, plus RBV resulted in 93% and 47% SVR in treatment-naïve HCV genotype 1 patients and in previous null-responders to PEG-IFN α plus RBV alone, respectively (Poordad 2013). Furthermore, in the single arm Pilot study evaluating ABT-450 in combination with the NNI ABT-072 plus ribavirin, SVR was achieved in 91% (10/11) of treatment-

naïve HCV genotype 1 patients, all of whom had the "good-response" IL28B genotype (Lawitz 2012). Importantly, a single patient in Pilot who achieved SVR 24 weeks after treatment completion experienced a late viral relapse between weeks 24 and 36 post-treatment. Sequencing analyses in this patient identified a resistant mutant in NS5B, possibly indicating that interferon-free treatment regimens may require longer follow-up times than conventional PEG-IFN α and ribavirin therapy. Sequencing analyses in patients who experienced viral breakthrough during treatment or early relapse after therapy (in Pilot or Co-Pilot) indentified resistance variants in both NS3 and NS5B. Interestingly, in NS3 substitutions were predominantly observed at position D168, whereas R155K was identified only in a single patient.

Combinations of NS3/4A inhibitors and NS5A inhibitors

The first clinical trial to report SVR data for an interferon-free regimen investigated the combination of the NS5A inhibitor daclatasvir with the NS3/4A protease inhibitor asunaprevir for 24 weeks in 10 HCV genotype 1 patients with prior null response to PEG-IFN α plus RBV (Lok 2012). 36% of patients achieved SVR. Importantly, viral breakthrough was observed only in patients infected with HCV genotype 1a, and in all of them resistance mutations against both agents were identified. Nevertheless, this trial constituted a proof-of-principle that SVR can be achieved by all-oral regimens, especially in patients infected with HCV subtype 1b. This has been confirmed in a larger follow-up study (Lok 2012), as well as by a 100% SVR rate in a small study evaluating the same agents (daclatasvir plus asunaprevir) in Japanese HCV genotype 1b infected previous null responder patients (Chayama 2012), and in a subsequent Japanese study in HCV genotype 1b patients with prior null response (n=21) or ineligibility to IFN (n=22), in whom SVR rates of 91% and 64% were seen, respectively (Suzuki 2012). For HCV gentoype 1a patients, promising data were presented for a more potent all-

oral regimen including daclatasvir, asunaprevir plus the NNI BMS-791325 (see below).

Combinations of NS5A inhibitors and nucleoside analog NS5B inhibitors plus ribavirin

Impressive results have been shown for the combination of the NS5A inhibitor daclatasvir with the NI sofosbuvir, with or without ribavirin for 24 weeks (Sulkowski 2012). In approximately 90 treatment-naïve patients, RVR and SVR rates were 100% and 100% in HCV genotype 1 patients, and 100% and 86-88% in HCV genotype 2 and 3 patients, respectively. In this study, the addition of RBV did not improve virologic response rates but resulted in anemia in a significant proportion of patients. Furthermore, an unfavorable IL28B genotype apparently did not decrease the chance of cure in this study.

Combinations of multiple DAAs with or without ribavirin

According to a preliminary analysis of a study evaluating a multiple DAA regimen, namely the combination of the NS5A inhibitor GS-5885, the NS3/4A inhibitor GS-9451, the NNI tegobuvir plus RBV was recently presented (Sulkowski 2012). In this so-called QUAD study, treatment-naïve HCV genotype 1 patients were treated for 12-24 weeks with this all-oral quadruple regimen. Patients were switched to a PEG-IFN α-based rescue therapy if HCV RNA did not fall below the limit of detection until treatment week 2. Approximately 70% of all patients were eligible for all-oral therapy in this study, and of those, at least 77% and 89% of HCV genotype 1a and 1b patients achieved SVR, respectively.

Another study evaluating an all-oral quadruple therapy included the NS3/4A protease inhibitor ABT-450/r, the NS5A inhibitor ABT-267, the NNI ABT-333, plus ribavirin. Strikingly, this regimen administered for 12 weeks led to SVR in 99% and 93% of treatment-naïve and prior null responders with HCV genotype 1 infection, respectively (Kowdley 2012).

An interferon-free, ribavirin-free study included the NS3/4A protease inhibitor asunaprevir in combination with the NS5A inhibitor daclatasvir and the NNI BMS-791325 for 12-24 weeks in treatment-naïve HCV genotype 1 patients, including a significant proportion of HCV subtype 1a patients. According to a preliminary report, 12 weeks of therapy resulted in an overall SVR rate of 94% of patients (Everson 2012).

Cyclophilin inhibitor-based therapies

The VITAL-1 Phase IIb clinical study evaluated the cyclophilin inhibitor alisporivir with or without RBV for 24 weeks in treatment-naïve HCV genotype 2 and 3, complemented by the addition of PEG-IFN α if RVR was not achieved (Pawlotsky 2012). SVR rates in the per protocol analysis were approximately 90% in patients treated with alisporivir plus RBV, and 70% in patients treated with alisporivir alone, but only 29-42% of all patients were eligible for treatment with all-oral therapy. Alisporivir resistance was rarely observed in patients with virologic failure.

Novel interferons

Over the 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 PEG-IFN lambda 1. Like other type 3 interferons, IFN lambda 1, also called interleukin-29 (IL-29), binds to a different receptor than IFN α, but downstream the 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). Interferon lambda was well-tolerated and the

majority of patients achieved 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 resulted in approximately 10% higher RVR and approximately 20% higher cEVR rates, a lower frequency of flu-like symptoms, but with more frequent aminotransferase and bilirubin elevations than PEG-IFN α-2a (Zeuzem 2011). There is now a full Phase III development plan for IFN lambda with DAAs.

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 plus 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, NI NS5B inhibitors, and NS5A inhibitors may have even more favorable properties than telaprevir and boceprevir in terms of HCV genotype coverage and safety profiles, less pronounced drug-drug interactions, and even possible once-daily administration.

However, the triple therapy approach has several limitations. First of all, concomitant IFN α plus ribavirin are necessary to avoid the development of antiviral resistance. Consequently, the 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 DAA combinations in quadruple treatment regimens will likely be a very potent option

for difficult-to-cure patient populations such as HCV gentoype 1a patients with prior null response.

Furthermore, impressive data have clearly shown that numerous patients will likely have the chance to be cured by the all-oral IFN-free treatment regimens. In such interferon-free combination regimens, the inclusion of drugs with a high genetic barrier to resistance such as nucleoside NS5B inhibitors as well as of drugs with a high antiviral efficacy such as NS3/4A or NS5A inhibitors appears to be important. Intensive research will be necessary to determine which treatment regimen is optimal in terms of safety and efficacy in individual patients.

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. First we will discuss adverse events associated with dual therapy with interferon and ribavirin and later address the adverse events with boceprevir and telaprevir.

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 needs 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 edema 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

	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	
>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). In the largest trial to date, the overall incidence of depression, major depression and severe depression was significantly lower in patients who recievd a preemptive antidepressant therapy (Schaefer 2012). A second trial also showed less depressive symptoms in patients with escitalopram pre-treatment (de Knegt 2011).

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. In general G-CSF can be used to correct neutropenia, but 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
Anemia, asthenia, fatigue	First few weeks of treatment/ D: Increases over time	Erythropoietin, reduce RBV dosage, red blood cell transfusion, antidepressants, tryptophan, odanestron	

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	Edema of resp. mucosa / D: On treatment	Local therapy of fluticasone or budesonide	
Hypothyroidism	IFN / 3-10% reversible on discontinuation	Substitution of thyroid hormone	
Hyper-thyroidism	1-3%	B-blockers, carbimazole	
Psychiatric effects	On IFN, pre-existing[1] or not[6]	SSRIs (citalopram[2], paroxetin) Mirtazapine[3] Nortriptyline[4] Tricyclics (doxepine)	Tricyclics are 2nd choice – interactions and delirium, heart, liver complications
Agitation/ aggression		Antipsychotics (risperidone, olanzapine)	Monitor with psychiatrist

Symptom	When/why/ Duration (D)	Treatments	Caution
Severe sleep disturbances, irritability, depression		Benzodiazapines[5], zolpidem, trimipramine	[5]Can induce addiction
Hemolytic anemia	RBV	RBV dose reduction RBC transfusion Erythropoetin[7]	
Thrombo-cytopenia	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

Boceprevir has to be taken three times a day with food. Telaprevir has to be taken with a fat-containing meal two or three times a day. Pill burden is high with 12 pills for boceprevir and 6 for telaprevir. Dosing and taking the medication not fasting are crucial for efficacy. Boceprevir or telaprevir doses should never be reduced in case of toxicities, but rather discontinued or kept at the standard dose. Reducing the dose of these HCV protease inhibitors will result in treatment failure due to lower drug exposure.

Frequent adverse events seen with **telaprevir** are itching and rash, with the first occurring in the majority of patients (Jacobson 2011, McHutchinson 2010). Itching can be orally treated with antihistamines, eg, cetirizine, but efficacy seems limited. Rash is usually mild to moderate while serious skin reactions seem to be rare. Discontinuation is rarely necessary. Use of corticosteroid-based ointments, eg, prednicarbate 0.4% 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.

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. Anal fissures can be treated with nitroglycerine ointment or diltiazem hydrochloride 2% ointment.

A more frequent and more pronounced anemia than what is seen with interferon plus ribavirin may require early dose adjustment of ribavirin or red blood cell transfusion. Early dose reduction of ribavirin does not seem to reduce efficacy (pooled analysis of the ADVANCE and ILLUMINATE study, Janssen data on file). 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 on telaprevir and may require symptomatic therapy (Hézode 2009, McHutchison 2009, McHutchison 2010, Marcellin 2010).

Table 6.5 – Adverse event profile associated with telaprevir (Jacobson 2011) and boceprevir (Poordad 2011) in therapy-naive patients in clinical studies

Telaprevir (ADVANCE study)	TLP + PEG-IFN α-2a + RBV	PEG-IFN α-2a + RBV
Serious adverse event	11%	9%
Discontinuation due to adverse event	7%	4%
Anemia (<10g/dl)	45%	16%
Rash	37%	24%
Itching	50%	36%
Anal discomfort/pruritis	17%	4%
Boceprevir (SPRINT-2 study)	**BOC + PEG-IFN α-2b + RBV**	**PEG-IFN α-2b + RBV**
Serious adverse event	11%	9%
Discontinuation due to adverse event	12%	16%
Anemia (<10 g/dl)	49%	29%
Dysgeusia	37%	18%

Table 6.6 – Common side effects (>5% of patients) recorded in the PEG-IFN/RBV/PI Phase II & III trials. The incidence of side effects between different studies is difficult to compare because there were significant differences in genetic and socioeconomic backgrounds, as well as methodological differences in assessing side effects. 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

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 (Bacon 2011, Poordad 2011). Again, early ribavirin dose reduction in patients with a considerable decline in hemoglobin is possible without

reducing efficacy. The use of erythropoietin does not seem to result in higher antiviral efficacy compared to ribavirin dose reduction (Sulkowski 2012).

Dysgeusia is another frequent complaint that resolves upon discontinuation (Bacon 2011, Poordad 2011).

In one study including patients with compensated liver cirrhosis treated with telaprevir or boceprevir an unexpected proportion of serious adverse events (up to 50% of the patients) was observed including sepsis, hepatic decompensation and death (Hézode 2012). Preliminary data from other cohort studies presented at recent conferences suggest better safety outcomes in cirrhotic patients possibly due to a more cautious use of triple therapy.

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 an interactive 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

Albrecht Böhlig, Karl-Philipp Puchner 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 (in particular, Hashimoto thyroiditis)
	Insulin resistance/diabetes mellitus*
	GH insufficiency
	Vitamin D deficiency
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
Central nervous system disorders	Chronic fatigue*, subclinical cognitive impairment, psychomotoric deceleration, symptoms of depression*
	Neurocognitive disorders
Miscellaneous	Myopathy
	Cardiomyopathy/Myocarditis
	Idiopathic pulmonal fibrosis

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

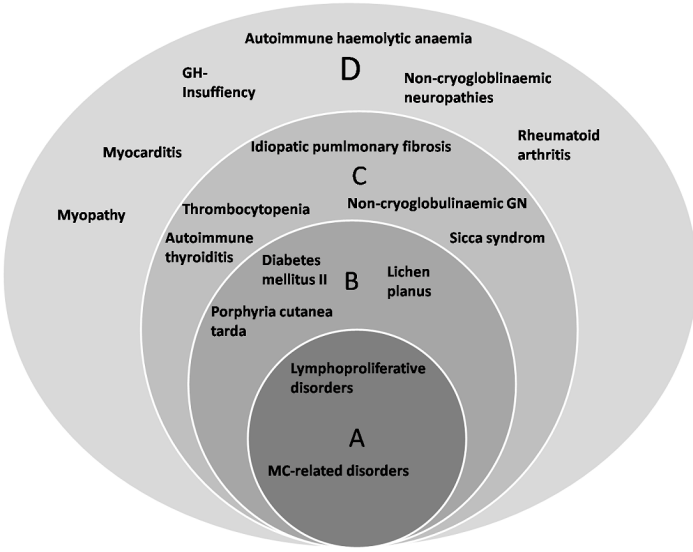

Figure 7.1 – Schematic representation of EHM categories (modified after Zignego 2007a). A) Associations with strong epidemiological evidence and clear pathogenetic mechanisms; B) Associations with high prevalence, but unclear pathogenetic mechanisms; C) Associations for which high prevalence in HCV could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

Lymphoproliferative disorders

Cryoglobulinemia refers to the presence of abnormal immunoglobulins in the serum. Cryoglobulins (CGs) are classified into three types. Type II CGs, 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 cryoglobulinemia 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).

Table 7.2 – Diagnostic criteria of cryoglobulinemic 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 evolves 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-IFN plus ribavirin as compared to PEG-IFN 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).

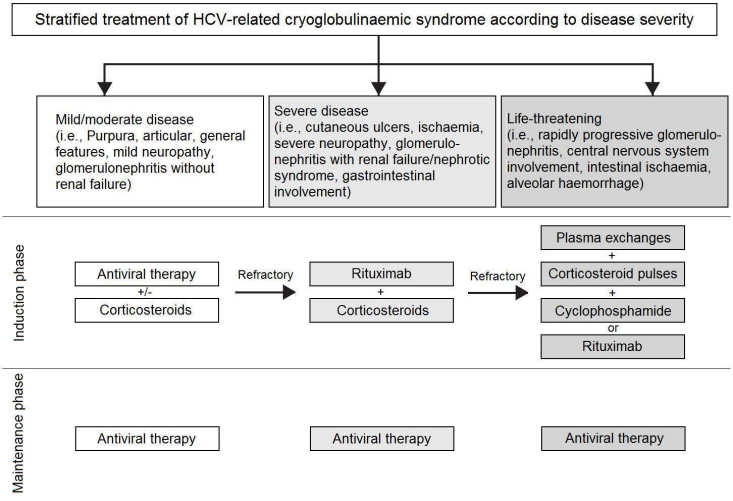

Figure 7.2 – Therapy algorithm for symptomatic HCV-related mixed cryoglobulinemia (modified according to Ramos-Casals 2012). In patients with severe manifestations, treatment should focus on immunosupression with rituximab (± plasmapheresis).

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, as the FDA recently approved a new indication for elthrombopag for patients with thrombocytopenia with chronic hepatitis C to allow the initiation and maintenance of interferon-based

therapy (FDA website, accessed 22 January 2013). 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 cyclophosphamide 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.

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	
Ischemic and hemorrhagic strokes	Younger HCV patients	
Transverse myopathies/ symmetrical paraparesis/ 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

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).

Numerous **central nervous system** manifestations have been described associated with HCV infection. Manifestations range from cryoglobulinemic and non-cryoglobulinemic vasculitis of cerebral blood vessels (Cacoub 1998) via chronic fatigue to depression with evidence that antiviral therapy can lead to elevation of tryptophan blood levels contributing to amelioration of depressive symptoms in HCV patients (Zignego 2007c). Cognitive dysfunction seems to rely on direct viral

neurotoxic effects and induction of cerebral and/or systemic inflammation (Senzolo 2011).

8. Management of HCV/HIV Coinfection

Christoph Boesecke, Stefan Mauss and Jürgen Kurt Rockstroh

Epidemiology of HIV/ HCV coinfection

Of the 34 million HIV-infected persons worldwide in 2010 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, Rockstroh 2012). 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%
Belarus, 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.

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 formula for converting the amount of HCV RNA in copies/ml to 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 anti-ANA with homogeneous pattern should be evaluated for concurrent autoimmune hepatitis, especially in the presence of ALT elevation while on treatment.

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). 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, confirms 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+ 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 patients with HCV genotypes 2, 3 and 4 infection and in patients with genotype 1 infection where the new HCV protease inhibitors are not available.

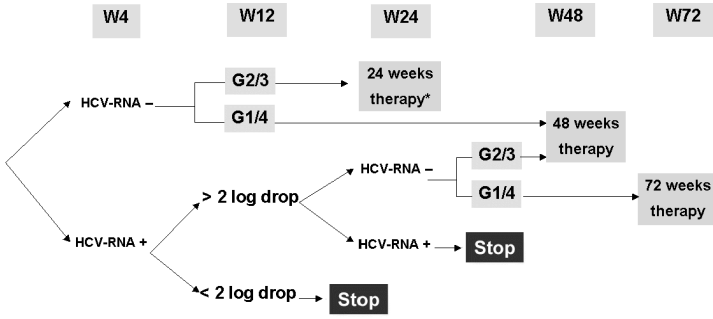

Figure 8.1 – Proposed optimal duration of hepatitis C virus (HCV) therapy in HIV/HCV-coinfected patients treated with pegylated interferon and ribavirin (for genotype 1 infection only when HCV PIs are not available) (W:week; G:genotype) (modified from Rockstroh 2009)

*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. Therapy is particularly recommended in patients with a high likelihood of achieving an SVR, ie, patients infected with genotype 2 or 3 and those infected with genotype 1 with an IL28B CC genotype or GT 1 patients with a previous relapse under dual therapy which now can be retreated with triple therapy (EACS 2012). 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 first pilot studies in HIV/HCV-coinfected individuals with HCV genotype 1 demonstrating significantly higher SVR12 rates with triple therapy compared to dual therapy, HCV protease inhibitor-based therapy with either boceprevir or telaprevir is now the new standard of care in HCV genotype 1 infection in HIV-infected individuals, where available. Telaprevir is added to PEG-IFN/RBV treatment for 12 weeks at 750 mg every 8 hours. In case of successful treatment response at week 4 (HCV RNA <1000 IU/mL), telaprevir should be continued until week 12. If HCV RNA at week 12 is still <1000 IU/mL, dual therapy with PEG-IFN/RBV should be continued until week 24. If HCV RNA is undetectable at week 24, dual therapy with PEG-IFN/RBV should be continued for another 24 weeks resulting in a total treatment duration of 48 weeks.

Boceprevir can be added to PEG-IFN/RBV after a lead in of 4 weeks of PEG-IFN/RBV dual therapy. In case of an HCV RNA >100 copies/mL at week 12 or a detectable HCV RNA at week 24, all HCV therapy needs to be discontinued and interpreted as lack of response and as high risk for boceprevir resistance selection. Overall treatment duration of a boceprevir-based therapy is 48 weeks. Considering the complex treatment issues, in particular drug-drug interactions (see below), inclusion into clinical trials should be preferred, and close monitoring for patients treated outside of trials is highly recommended. The use of the new HCV

PIs is associated with additional toxicities, in particular higher rates of anemia for both drugs, rash and anal itching for telaprevir and dysgeusia for boceprevir. Anemia management is therefore very important and requires more frequent monitoring of hemoglobin levels during the first weeks of HCV treatment. Early ribavirin reduction and EPO use have both been demonstrated to be effective in anemia management while not lowering overall SVR rates. Data from monoinfected subjects with cirrhosis suggest even higher anemia rates and blood cell counts need to be determined in such patients at least every 2 weeks after starting HCV therapy. In addition, careful surveillance should be addressed regarding severe infectious complications including deaths due to sepsis and liver decompensation, observed in 3-8% of monoinfected cirrhotic patients on triple therapy in an observational study where a mortality rate greater than 1% was recorded. Data in HIV/HCV-coinfected patients with cirrhosis is still lacking.

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). Due to drug-drug interactions, telaprevir can currently only be safely combined with boosted atazanavir, raltegravir, rilpivirine, etravirine or efavirenz (with efavirenz, telaprevir doses need to be increased to 1125 mg every 8 hours). Using tenofovir or abacavir in combination with emtricitabine or lamivudine as backbone seems safe. Due to drug-drug interactions, boceprevir can only be currently safely combined

with raltegravir or etravirine in combination with tenofovir or abacavir and emtricitabine or lamivudine. The EMA has also suggested considering boceprevir in combination with boosted atazanavir on a case-by-case basis in patients with no previous HIV treatment failure and no drug resistance who have suppressed HIV RNA when starting HCV therapy.

Table 8.4 summarizes possible interventions for HCV/HIV-coinfected non-responders and relapsers to previous interferon-based therapies.

Liver transplant 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 overuse, 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.

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 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)	For genotype 1 patients, wait and monitor if low levels of fibrosis (F0/1) and no or little progression, otherwise retreat with triple therapy. For genotypes 2, 3 and 4 for patients with mild fibrosis, wait and monitor. If rapid progression or >moderate fibrosis, retreatment using combination therapy with PEG-IFN plus weight-based ribavirin dosing (consider longer treatment duration)
	2. Non-response (no HCV RNA negativization during treatment)	For G1 patients with F3/4 fibrosis or those with other stages of fibrosis and rapid progression, consider triple therapy treatment with telaprevir or boceprevir. In patients without a 2 log decrease of HCV RNA or with no data on HCV RNA decrease in the previous treatment cycle, triple therapy is recommended if there is an HCV RNA decrease of 1 log after a 4-week lead in with PEG-IFN/RBV. For others, monitor carefully and wait until new antivirals become available through clinical trials or are approved

*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.

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). In contrast, NNRTIs can lower the concentrations of immunosuppressive drugs.

Conclusion

HIV has been shown to accelerate the progression of hepatitis C resulting in higher liver disease-related mortality and morbidity in HIV/HCV-coinfected patients compared to HCV- or HIV-monoinfected individuals. For HCV genotype 2, 3 and 4 infection dual therapy comprising PEG-IFN plus ribavirin is still the current gold standard allowing sustained virologic response rates of almost 50% in HIV/HCV-coinfected individuals under optimized management conditions (weight-based ribavirin and individualized treatment duration). For HCV genotype 1 infection, triple therapy with PEG-IFN, ribavirin and either telaprevir or boceprevir is now the standard allowing sustained virologic response rates of almost 70% in HIV/HCV-coinfected individuals. Drug-drug interactions between HAART, ribavirin and especially the new HCV protease inhibitors require careful selection of both HIV and HCV drugs as well as subsequent close monitoring.

To date, therapeutic options for patients with previous non-response to dual therapy are still very limited. However, first results from ongoing pilot trials of quadruple therapy combining PEG-IFN, ribavirin and two direct acting antivirals or early data for interferon-free regimens in HCV monoinfection give reason to expect new treatment regimens for this hard-to-treat patient population in the coming years.

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 (ie, 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, one 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, ie, 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. However, recent studies show that combination therapy with PEG-IFN and ribavirin is even more efficient in inducing virological respone as supported by a recently published meta-analysis study (Liu 2012). Close monitoring of both viruses is recommended during and after combination therapy. The introduction of new direct acting antivirals has opened new pathways in the treatment of HCV, which need to be evaluated in HBV/HCV-coinfected patients. However, currently no data exists for telaprevir and boceprevir, which have recently been approved for the treatment of HCV genotype 1 infection.

In patients with dominance of HBV disease, IFN +/- HBV polymerase inhibitors is an option currently being investigated. A recent study looked at tolerability and efficacy of several anti-HBV nucleos(t)ide analogs (lamivudine plus adefovir, entecavir, telbivudine, tenofovir disoproxil fumarate) (Coppola 2013). Clearance of HBV DNA was found in 96% of patients after 18 months, while HCV reactivation was low (12.5%). However, deterioration of liver cirrhosis was seen in as many as 33% of the participants. Patients who were HCV RNA positive at baseline deteriorated more frequently.

In HBV/HCV cirrhotic patients with detectable HCV RNA treatment with nucleos(t)ide analogs alone has a high risk of

clinical failure. However, further studies are needed to estimate the treatment value of these drugs in different clinical scenarios.

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 PEG-IFN plus ribavirin should be the treatment of choice. Treatment with the new DAA agents is now being studied, and 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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