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Short Guide to Hepatitis C

2011

edited by
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Short Guide to Hepatitis C

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The Flying Publisher

Short Guide to Hepatitis C

2011 Edition

Flying Publisher

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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 on the horizon. And because the virus affects such a large and varying population – some 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 **2011 Short Guide to Hepatitis C**, which is an expansion and update of the HCV chapters in **Hepatology – A Clinical Textbook** (2010), also published by Flying Publisher. As always, we invite qualified people everywhere to translate this book into other languages, and then make them available widely. This web-based free-of-charge concept is made possible by unrestricted 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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Abbreviations

ADV: adefovir dipivoxil
AHA: autoimmune haemolytic anaemia
ALT: alanine aminotransferase
AST: aspartate aminotransferase
BID: twice a day
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 α: interferon α
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
TSH: thyroid stimulating hormone

Table of Contents

1. Epidemiology, Transmission and Natural History 13
    Epidemiology 13
    Transmission 14
    Acute Hepatitis 15
    Chronic Hepatitis.....16
        Natural History 16
        Cirrhosis and Hepatic Decompensation 16
        Disease progression.....17

2. HCV - Structure and Viral Replication.....19
    Taxonomy and Genotypes 19
    Viral Structure 19
        Genome Organization 20
        HCV Proteins 21
    Viral Lifecycle 22
        Adsorption and viral entry 23
        Translation and posttranslational processes 23
        HCV RNA replication 24
        Assembly and release 25

3. Diagnostic Tests in Acute and Chronic Hepatitis C 26
    Serologic Assays 26
    Nucleic Acid Testing for HCV 27
    HCV Genotyping 29
    Implications for Diagnosis and Management 30
        Diagnosing acute hepatitis C 30
        Diagnosing chronic hepatitis C 31
        Diagnostics in the management of therapy 31

4. Hepatitis C Standard of Care 32
Treatment Goals and Definitions..... 33
Drugs.....34
Management of Chronic HCV Infection..... 35
Management of HCV genotype 2 and 3..... 36
Management of HCV genotype 1 37
Adherence..... 38
IL28B..... 39
Side effects 39
Interferon alfa (IFN).....39
Ribavirin.....42
Special populations 42
Patients with normal aminotransferase levels 42
HCV and liver transplantation..... 42
Dialysis patients 43
Retreatment.....43
Treatment of patients with prior antiviral treatment failure 43
Retreatment of patients with relapse after standard therapy..... 44
Retreatment of non-responders to standard therapy. 45
PEG-IFN maintenance therapy..... 45
Treatment of Acute Hepatitis C 46
Outlook..... 47

5. New Agents for Treating Hepatitis C.....48
Compounds targeting HCV polyprotein processing NS3-4A protease inhibitors..... 49
Telaprevir (VX-950)..... 51
Boceprevir (SCH 503034)..... 56
Ciluprevir (BILN 2061)..... 58
Other NS3-4A protease inhibitors..... 59
Resistance to NS3-4A protease inhibitors..... 59

Compounds Targeting HCV Replication....62
NS5B polymerase inhibitors.... 62
Nucleoside analogues.... 63
Non-nucleoside analogues.... 65
NS5A inhibitor.... 65
Combination therapies of specific antivirals....66
Host proteins as targets in treating hepatitis C.... 67
Cyclophilin B inhibitors.... 67
Nitazoxanide....68
Silibinin.... 68
Novel interferons.... 69
Outlook....69

6. Adverse Events and Drug Interactions 71
Systemic Symptoms....71
Psychiatric Adverse Events 72
Haematologic and immunologic effects....74
Skin disorders 74
Telaprevir and Boceprevir....77
Conclusion 77

7. Extrahepatic Manifestations 78
Lymphoproliferative Disorders 79
Malignant Lymphoproliferative Disorders/NHL 81
Treatment of Lymphoproliferative Disorders 82
Other Haematological Manifestations 84
Dermatologic and Other Manifestations....86

8. Management of HCV/HIV Coinfection 87
Epidemiology of HIV and HCV Coinfection 87
Diagnosing HCV in HIV Coinfection 88
The Natural History of Hepatitis C in HIV-Positive Patients
....89
Effect of Hepatitis C on HIV Infection 89
Effect of HAART on Hepatitis C 90

Treatment..... 90
Antiretrovirals while on HCV therapy..... 93
Liver Transplantation in HIV/HCV-Coinfected Patients . 94
Conclusion 95

9. Management of HBV/HCV Coinfection 96
Epidemiology.....96
Screening 97
Viral Interactions 97
Treatment 99
Conclusion 100

10. References.....102

11. Appendix.....120

1. Epidemiology, Transmission and Natural History

Jan-Christian Wasmuth

Epidemiology

Hepatitis C is a disease with a significant global impact. According to the World Health Organization there are 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 20%. In Africa and the Western Pacific the prevalence is significantly higher than in North America and Europe (Anonymous 2004). It is estimated that there are 2-5 million HCV-positive persons in Europe. Certain groups are preferentially affected, like injection drug users. In Europe and the United States chronic hepatitis C is the most common chronic liver disease. The majority of liver transplants performed in these regions are for chronic HCV. It is difficult to determine the number of new HCV infections, as most acute cases are not noticed clinically.

Transmission

Parenteral exposure to the hepatitis C virus is the most efficient means of transmission. The majority of patients infected with HCV in Europe and the United States acquired the disease through intravenous drug use or blood transfusion, 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.

The risk of perinatal transmission of HCV in HCV RNA positive mothers is estimated to be 5% or less (Ohto 1994). Caesarean

section has not been shown to reduce transmission. There is no evidence that breastfeeding is a risk factor.

Hemodialysis risk factors include blood transfusions, the duration of hemodialysis, the prevalence of HCV infection in the dialysis unit, and the type of dialysis. The risk is higher with in-hospital hemodialysis vs peritoneal dialysis.

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

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

Acute Hepatitis

After HCV inoculation, there is a variable incubation period. HCV RNA in blood (or liver) can be detected by PCR within several days to eight weeks (Hoofnagle 1997). Aminotransferases become elevated approximately 6-12 weeks after exposure (range 1-26 weeks) and they tend to be more than 10-30 times the upper limit of normal. HCV antibodies can be found about 8 weeks after exposure although it may take several months. However, the majority of newly infected patients will be asymptomatic and have a clinically non-apparent or mild course. Periodic screening for infection may be warranted in certain groups of patients who are at high risk for 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% (de Ledinghen 2007, Poynard 1997, Sangiovanni 2006, Wiese 2000). About 30% of patients will not develop cirrhosis for at least 50 years (Poynard 1997). It is not completely understood why there are such differences in disease progression. An influence of host and viral factors has to be assumed.

Cirrhosis and Hepatic Decompensation

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

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

Disease progression

Chronic HCV progression may differ due to 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).

Alcohol intake: Even moderate amounts of alcohol increase HCV replication, enhance the progression of chronic HCV, and accelerate liver injury (Gitto 2008).

Daily use of marijuana: may cause a more rapid progression.

Other host factors: TGF B1 phenotype and fibrosis stage are correlated with fibrosis progression rate. Moderate to severe steatosis correlates with developing hepatic fibrosis.

Viral coinfection: 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).

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.

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 in the near future. An online calculator and further information can be found at the website of The United Network for Organ Sharing (UNOS) (http://www.unos.org).

For details on extrahepatic manifestations, please see Chapter 7.

2. HCV - Structure and Viral Replication

Bernd Kupfer

Taxonomy and Genotypes

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

Viral Structure

Structural analyses of HCV virions are very limited because for a long time the virus was difficult to cultivate in cell culture systems, a prerequisite for yielding sufficient virions for electron microscopy. Moreover, serum-derived virus particles are associated with serum low-density lipoproteins (Thomssen

1992), which makes it difficult to isolate virions from serum/plasma of subjects via centrifugation.

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

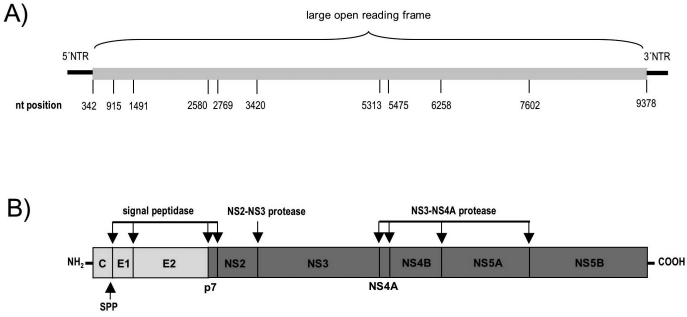

Figure 2.1. Genome organization and polyprotein processing. A) Nucleotide positions correspond to the HCV strain H77 genotype 1a, accession number NC_004102. nt, nucleotide; NTR, nontranslated region. B) Cleavage sites within the HCV precursor polyprotein for the cellular signal peptidase, the signal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

Genome Organization

The genome of the hepatitis C virus consists of one 9.6 kb single-stranded RNA molecule with positive polarity. Similar to other positive-strand RNA viruses, the genomic RNA of hepatitis C virus serves as messenger RNA (mRNA) for the translation of viral proteins. The linear molecule contains a single open reading frame (ORF) coding for a precursor polyprotein of

approximately 3000 amino acid residues flanked by two regulatory nontranslated regions (NTR) (Figure 2.1).

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

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

HCV Proteins

Translation of the HCV polyprotein is initiated through involvement of some domains in the NTRs of the genomic HCV RNA. The resulting polyprotein consists of ten proteins that are

co-translationally or post-translationally cleaved from the polyprotein. In addition, the F (frameshift) or ARF (alternate reading frame) protein has been explored (Walewski 2001). During translation ARFP is the product of ribosomal frameshifting within the core protein-encoding region.

Viral Lifecycle

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

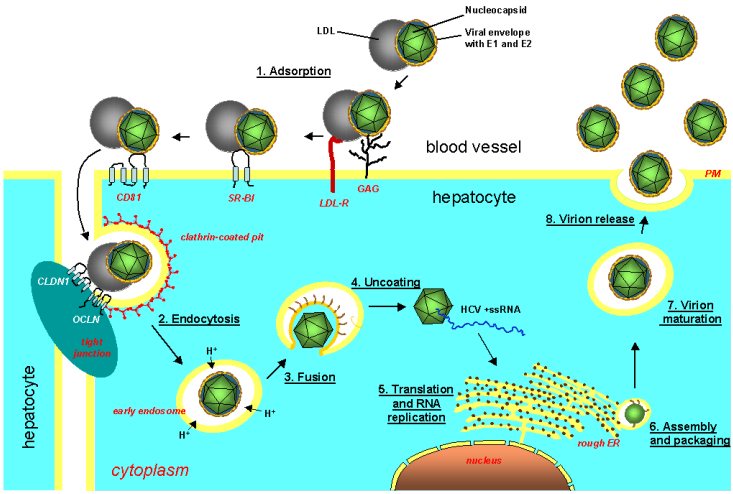

Figure 2.2. Model of the HCV lifecycle. Designations of cellular components are in italics. For a detailed illustration of viral translation and RNA replication, see Pawlotsky 2007. HCV +ssRNA, single stranded genomic HCV RNA with positive polarity; rough ER, rough endoplasmic reticulum; PM, plasma membrane.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

Adsorption and viral entry

Entry of HCV into a target cell is complex. A cascade of virus-cell interactions is necessary for the infection of hepatocytes and the precise mechanism of viral entry is 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 occluding (OCLN) have been shown to interact with HCV (Evans 2007, Ploss 2009). Although the precise mechanism of HCV uptake in hepatocytes is still not clarified, these cellular components may represent the complete set of host cell factors necessary for cell-free HCV entry. Interaction of HCV with CLDN1 and OCLN seems to induce the internalisation of the virion via clathrin-mediated endocytosis (Hsu 2003). Subsequent HCV E1-E2 glycoprotein mediation fuses the viral envelope with the endosome membrane (Meertens 2006).

Translation and posttranslational processes

As a result of the fusion of the viral envelope and the endosomic membrane, the genomic HCV RNA is released into the cytoplasm of the cell (uncoating). The viral genomic RNA possesses a nontranslated region (NTR) at each terminus. It contains an internal ribosome entry side (IRES) involved in

ribosome-binding and subsequent initiation of translation (Tsukiyama-Kohara 1992). The synthesized HCV precursor polyprotein is subsequently processed by at least four distinct peptidases. The cellular signal peptidase (SP) cleaves the N-terminal viral protein's immature core protein, E1, E2, and p7 (Hijikata 1991), while the cellular signal peptide peptidase (SPP) is responsible for the cleavage of the E1 signal sequence from the C-terminus of the immature core protein, resulting in the mature form of the core (McLauchlan 2002). The E1 and E2 proteins remain within the lumen of the ER where they are subsequently N-glycosylated with E1 having 5 and E2 harbouring 11 putative N-glycosylation sites (Duvet 2002). The remaining HCV proteins are posttranslationally cleaved by the viral NS2-NS3 and the NS3-NS4A protease, respectively.

HCV RNA replication

The complex 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.

3. Diagnostic Tests in Acute and Chronic Hepatitis C

Christian Lange and Christoph Sarrazin

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

Serologic Assays

With 2nd generation enzyme-linked immunoassays (EIAs), HCV-specific antibodies can be detected approximately 10 weeks after infection (Pawlotsky 2003b). To narrow the diagnostic window from viral transmission to positive serological results, a 3rd generation EIA has been introduced that includes an antigen from the NS5 region and/or the substitution of a highly immunogenic NS3 epitope, allowing the detection of anti-HCV antibodies approximately four to six weeks after infection with a sensitivity of more than 99% (Colin 2001). Anti-HCV IgM measurement can narrow the diagnostic window in only a

minority of patients and cannot discriminate between acute and chronic hepatitis C.

False-positive results are more frequent in patients with rheuma factors and in populations with a low hepatitis C prevalence, for example in blood and organ donors. False-negative HCV antibody testing may occur in patients on haemodialysis or in severely immunosuppressed patients or in haematological 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 equivalent sensitivity for determination of chronic hepatitis C as HCV RNA measurement (Morota 2009). Overall, the sensitivity of the core antigen assay is lower in comparison to highly sensitive HCV RNA assays and data on the potential use of the core antigen assay instead of HCV RNA tests for management of antiviral therapy have not been presented yet.

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 Molecular Systems, USA) is an FDA- and CE-approved RT-PCR system for qualitative HCV RNA testing that allows detection of HCV RNA concentrations down to 50 IU/ml of all HCV genotypes (Nolte 2001).

Transcription-mediated amplification- **(TMA)-based qualitative HCV RNA detection** has a very high sensitivity (lower limit

of detection 5-10 IU/ml) (Sarrazin 2002, Hendricks 2003). A commercially available TMA assay is the Versant™ HCV RNA Qualitative Assay (Siemens Medical Solutions Diagnostics, Germany). This system is accredited by FDA and CE and provides an extremely high sensitivity, superior to RT-PCR-based qualitative HCV RNA detection assays (Sarrazin 2000, Sarrazin 2001, Hofmann 2005).

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

All commercially available HCV RNA assays are calibrated to the WHO standard based on HCV genotype 1. It has been shown that results may vary significantly between assays with different HCV genotypes despite standardisation (Chevaliez 2007, Vehrmeren 2008).

The **Cobas TaqMan** (Roche Diagnostics) assay makes both highly sensitive qualitative (limit of detection approx. 10 IU/ml) and linear quantitative HCV RNA detection (35-107 IU/ml) feasible with high specificity and excellent performance in one system with complete automation.

The **Abbott RealTime**™ HCV Test provides a lower limit of detection of 12 IU/ml, a specificity of more than 99.5% and a

linear amplification range from 12 to 10,000,000 IU/ml independent of the HCV genotype (Michelin 2007, Sabato 2007, Schutten 2007, Vermehren 2008).

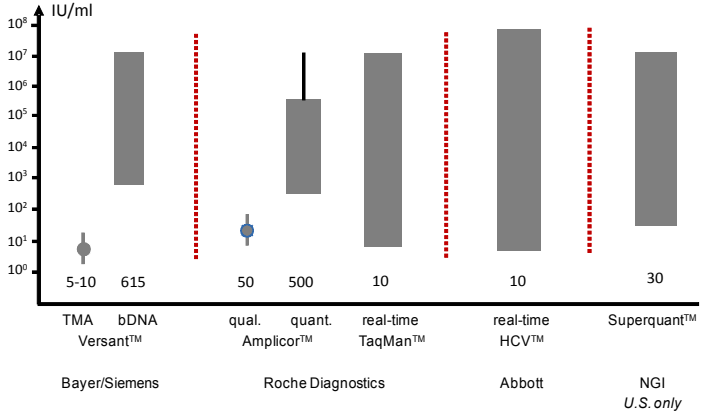

Figure 3.1. Detection limits and linear dynamic ranges of commercially available HCV RNA detection assays.

HCV Genotyping

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

The **Versant™ HCV Genotype 2.0 System** (Siemens Medical Solutions Diagnostics) 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 **Abbott RealTime™ HCV Genotype II** assay is based on real-time PCR technology, which is less time-consuming than direct sequencing. Preliminary data reveal a 96% concordance at the genotype level and a 93% concordance on the genotype 1 subtype level when compared to direct sequencing of the NS5B and 5'UTR regions.

Implications for Diagnosis and Management

Diagnosing acute hepatitis C

When acute hepatitis C is suspected, the presence of both anti-HCV antibodies and HCV RNA should be tested. For HCV RNA detection, sensitive qualitative techniques with a detection limit of 50 IU/ml or less are required, for example TMA, qualitative RT-PCR or the newly developed real-time PCR systems. HCV RNA may fluctuate during acute hepatitis C, making a second HCV RNA test necessary several weeks later in all negatively tested patients with a suspicion of acute hepatitis C. When HCV RNA is detected in seronegative patients, acute hepatitis C is very likely. When patients are positive for both anti-HCV antibodies and HCV RNA, it may be difficult to

discriminate between acute and acutely exacerbated chronic hepatitis C. Anti-HCV IgM detection will not suffice because its presence is common in both situations.

Diagnosing chronic hepatitis C

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

Diagnostics in the management of therapy

Exact HCV subtyping may gain increased importance for future use of direct-acting antiviral agents (DAA) because some HCV subtypes behave differently regarding antiviral activity and the development of resistance. Low HCV RNA concentrations (<600,000–800,000 IU/ml) at baseline is a positive predictor of a sustained virological response (SVR). The assessment of viral kinetics during treatment is important to predict the outcome of antiviral therapy and to determine individualized treatment durations.

Due to the differences in HCV RNA concentrations of up to a factor of 4 between the different commercially available assays, despite standardisation of the results to IU, and due to intra- and interassay variability of up to a factor of 2, it is recommended to always use the same assay in a given patient before, during and after treatment and to repeat HCV RNA measurements at baseline in cases with HCV RNA concentrations between 400,000 and 1,000,000 IU/ml.

4. Hepatitis C Standard of Care

Markus Cornberg, Michael P. Manns, Heiner Wedemeyer

The goal of antiviral hepatitis C therapy is to cure the infection via a sustained elimination of the virus (Veldt 2007) and to prevent liver fibrosis and end-stage liver diseases (cirrhosis and hepatocellular carcinoma). In 2011, this goal can be achieved in a great number of patients with a combination treatment of pegylated interferon and ribavirin. Treatment success depends on HCV genotype and patient characteristics, the best results being achieved in patients who have genotype 2 or 3 and lower pretreatment HCV RNA levels, and who are young and have no cirrhosis. Standard treatment varies from 6 to 12 months, but may be shorter in selected cases and longer in others. Under these circumstances, adherence is paramount. This, and frequent adverse drug effects, demand perseverance on behalf of patients and their physicians.

The following paragraphs describe the treatment of chronic hepatitis C in various settings. The chapter ends with a discussion of the promissing perspectives of treating acute hepatitis C infection.

Treatment Goals and Definitions

The measure of treatment success is the undetectability of HCV RNA. Treatment aims at achieving a sustained elimination of HCV, a sustained virological response (SVR), i.e., HCV RNA that remains negative six months after the end of treatment. More than 99% of patients who achieve an SVR remain HCV RNA negative 5 years after the end of treatment (Swain 2007). Another important step is the so-called rapid virologic response (RVR), defined as undetectable HCV RNA (= HCV RNA negative) after 4 weeks of treatment. Table 4.1 shows current abbreviations for therapeutic milestones.

Table 4.1 – Abbreviations and definitions of therapeutic milestones.

Abbreviation		Definition
RVR	Rapid virologic response	HCV RNA is undetectable (<50 IU/mL = HCV-RNA negative) 4 weeks after starting treatment.
eRVR	Extended rapid virologic response	HCV RNA is undetectable (<50 IU/mL) at treatment weeks 4 **and** 12
EVR	Early virologic response	HCV RNA is undetectable (<50 IU/mL) 12 weeks after starting treatment or drops by at least two logs.
cEVR	Complete early viral response	HCV RNA is undetectable (<50 IU/mL) 12 weeks after starting treatment.
pEVR	Partial early viral response	2 log decline of HCV RNA but no cEVR.
ETR	End of treatment response	HCV RNA is undetectable (<50 IU/mL) at the end of therapy.
SVR	Sustained viral response	HCV RNA is undectectable (<50 IU/mL) at the end of treatment **AND** 6 months later.
	Partial response	HCV RNA levels decline >2 log but never become undetectable.
	Nonresponse	HCV RNA levels fail to decline by at least 2 logs by 24 weeks.

Drugs

The treatment of choice is the combination of a once-weekly administered pegylated interferon α plus daily ribavirin (see also Appendix, Table 11.2). **PEG-IFN α-2b** (PEG-Intron®, (Merck) is given adjusted for body weight (1.5 µg/kg once weekly), while **PEG-IFN α-2a** (PEGASYS®, Roche) is given in a fixed dose of 180 µg once weekly (reviewed in Cornberg 2002, Pedder 2003). 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 (McHutchinson 2009, Manns 2009). Both pegylated interferons have comparable efficacy. Although some smaller trials suggest slightly higher SVR rates in patients treated with PEG-IFN α-2a (Rumi 2010, Ascione 2010), a large US multicenter study did not detect any significant difference between the two PEG-IFNs when combined with ribavirin (McHutchinson 2007).

Table 4.2 – Combination therapy of chronic hepatitis C (2011).

Drug	Dosing
1) Pegylated Interferon α-2a (Pegasys®)	180 µg once weekly
+	
Ribavirin (Copegus®)	<75 kg: 1000 mg (Genotype 1,4)
http://goo.gl/N04Tx	≥75 kg: 1200 mg (Genotype 1,4)
	800 mg (Genotype 2,3)
2) Pegylated Interferon α-2b (PEG-Intron®)	1.5 µg/kg once weekly
+	
Ribavirin (Rebetol®)	≤65: 800 mg
http://www.spfiles.com/pipeg-intron.pdf	66-80 kg: 1000 mg
	81-105 kg: 1200 mg
	>105 kg: 1400 mg

* Non-pegylated interferons include Interferon a-2a (Roferon®, dose: 3–4.5 mill IU three times weekly (TIW)); Interferon a-2b (Intron A®, dose: 3 mill IU TIW); and Consensus Interferon (Infergen®, dose: 9 µg TIW)

Ribavirin should be administered according to bodyweight. The standard dosage is shown in Table 4.2. When combined with PEG-IFN α-2a, a ribavirin (Copegus®) dose of 1000 mg if <75 kg or 1200 mg if ≥75 kg is recommended for HCV genotype 1 patients. For patients with HCV genotypes 2 or 3 a flat dose of 800 mg ribavirin is suggested (Table 4.2) (Hadziyannis 2004), as there is no additional benefit of higher ribavirin doses. However, relapse rates may increase with increasing body weight of the patient (Jacobson 2007). Therefore, for HCV genotype 2 or 3 patients a weight-based dose of ribavirin (12-15 mg/kg) may be preferred, especially when reducing the treatment duration (Schiffman 2007).

When combined with PEG-IFN α-2b, the optimal ribavirin (Rebetol®) dose is at least 11 mg/kg (Manns 2001). Another study confirmed that PEG-IFN α-2b plus weight-based ribavirin is more effective than flat-dose ribavirin, particularly in HCV genotype 1 patients (Jacobson 2007). A ribavirin dose of 15 mg/kg would be ideal, although higher doses are associated with higher rates of anaemia (Snoeck 2006).

Management of Chronic HCV Infection

The benefits of treatment must outweigh the risks. Patients who are at risk of developing end-stage liver disease are most likely to benefit from HCV therapy; this is especially true for patients who have a genotype 2 or 3 infection, a low level of viremia, and no co-morbid conditions.

Treatment duration should be tailored to the individual patient. While some patients with unfavorable baseline factors may need a longer treatment time to reach an SVR, patients with favorable baseline factors may be treated for a shorter period. Standard treatment duration is 24 weeks for patients with HCV genotype 2 and 3, and 48 weeks for patients with genotype 1.

Management of HCV genotype 2 and 3

The standard treatment duration for patients with genotype 2 or 3 infection is 24 weeks. Reduction to 12 to 16 weeks of treatment is possible in patients who have a baseline HCV RNA <800,000 IU/ml and a rapid virologic response (RVR), i.e., HCV RNA to <50 IU/ml after 4 weeks of treatment (Poustchi 2008, Dalgard 2008, Dalgard 2004, Mangia 2005) (Appendix, Table 11.3). Such shorter treatment schedules reveal that genotype 3 patients with low baseline viremia (<400-800.000 IU/ml) have a much better chance of responding than those with a higher viral load (>400-800.000 IU/ml) (Shiffman 2007; Poustchi 2008). Generally, patients with genotype 2 respond better than those with genotype 3 (Zeuzem 2004a) (Appendix, Table 11.2). Reducing treatment duration is not recommended in patients with advanced liver fibrosis or cirrhosis (Aghemo 2006), diabetes mellitus (Poustchi 2008b) or BMI >30 kg/m^2.

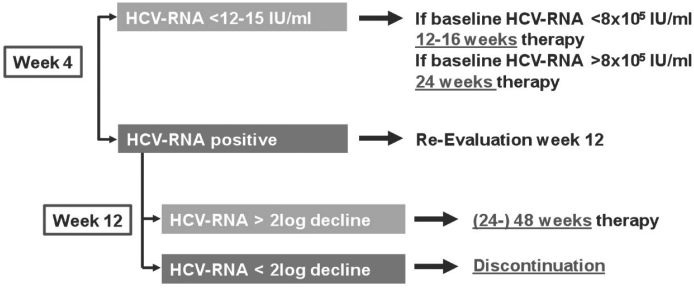

Figure 4.1 – Recommendation for treatment for HCV genotypes 2 and 3. Sensitive HCV RNA assays (limit of detection 12-15 IU/ml or 50 IU/ml) at weeks 4 and 12 may determine treatment duration. Reducing treatment duration is not recommended in patients with liver cirrhosis, insulin resistance or hepatic steatosis.

In contrast, HCV genotype 2/3 patients without an RVR (especially HCV genotype 3 and high viral load) may be treated

for longer than 24 weeks (i.e., 48 weeks); however, so far only retrospective analyses support this (Willems 2007).

Depending on the assay used to determine RVR, around 25-30% of HCV genotype 2/3 patients belong to this difficult-to-treat population not achieving RVR (Appendix, Table 11.4).

Figure 4.1 summarizes the treatment milestones. Patients with undetectable HCV RNA at **week 4** are scheduled to continue treatment for a total of 16 or 24 weeks, depending on their baseline HCV RNA. Patients who are still HCV RNA positive at week 4, are reevaluated at **week 12**. If HCV RNA decline from baseline is >2 $\log_{10}$, the duration of treatment is for at least 24 weeks, in some cases longer. When the HCV RNA decline is <2 $\log_{10}$, treatment should be discontinued.

Management of HCV genotype 1

HCV genotype 1 is more difficult to treat than genotypes 2 and 3. Standard treatment duration for genotype 1 infection is 48 weeks. The same is true for genotypes 4-6 infections because of limited data in these patients.

The first treatment milestone is **week 4**. In patients with undetectable HCV RNA at week 4 who had low viral load at baseline (HCV RNA <600,000 IU/ml), it is possible to reduce treatment duration to 24 weeks (Figure 4.2 and Appendix, Table 11.5). With higher baseline viral loads, treatment should continue through week 48. Patients with HCV genotype 1 and an HCV RNA decline of less than 2 $\log_{10}$ or HCV RNA >30,000 IU/ml HCV RNA at **week 12** are unlikely to achieve a sustained viral response (Davis 2003, Berg 2003); treatment should be discontinued. Treatment should also be stopped in patients with detectable HCV RNA at **week 24**. Patients who do achieve undetectable HCV RNA levels between week 12 and week 24 (pEVR) should continue treatment for up to 72 weeks. Extension to 72

weeks is likely to improve response rates for those with a slow viral response (>2 log_{10} decline but >50 IU/ml at week 12) (Berg 2009). 80/80/80 adherence and high patient motivation is mandatory.

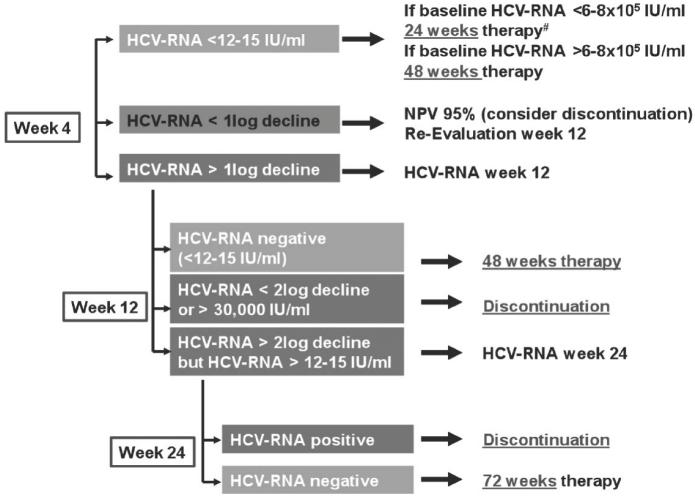

Figure 4.2 – Recommendation for treatment algorithm for HCV genotype 1. Also recommended for genotypes 4-6 because of limited data in these patients. Sensitive assays (limit of detection 12-15 or 50 IU/ml) at weeks 4, 12, 24 may determine treatment duration. Reduction is not recommended in patients with liver cirrhosis, insulin resistance or hepatic steatosis.

Adherence

Adherence to therapy is one of the most important factors associated with treatment success (McHutchinson 2002). The definition of adherence used is the "80/80/80 rule", that is, patients who receive more than 80% of the IFN, more than 80% of the ribavirin, 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 demonstrated that patients who fulfilled the 80/80/80 rule had a 63% SVR compared to 52% of those with less than 80% adherence (McHutchinson 2002). This was statistically significant for HCV genotype 1 patients. It is important to reduce side effects and motivate patients to adhere to treatment in order to optimize treatment response, especially in the difficult-to-treat genotype 1 patients.

IL28B

Recently, different nucleotide polymorphisms upstream of the IL28B gene have been associated with response to PEG-IFN and ribavirin and spontaneous clearance of acute HCV infection (reviewed by Afdhal 2011). In addition, genetic variants of inosine triphosphatase (ITPA) have been correlated with protection against ribavirin-induced haemolytic anaemia (Fellay 2010). It will be interesting to see how genetic markers will influence treatment decisions in the future. IL28B already impacts the design and interpretation of new clinical trials and may influence the process of regulatory approval for new anti-HCV therapeutic agents.

Side effects

Severe side effects may reduce adherence to therapy and result in dose modifications. As a consequence, treatment responses may be less than optimal (Table 4.3).

Interferon alfa (IFN)

The effect of IFN on bone marrow results in decreased granulocytes and thrombocytes during treatment. These effects are usually moderate if counts are normal at baseline. However, dose modifications will be necessary in patients with initially low

platelet counts. This limits the use of IFN in patients with advanced liver cirrhosis who are also more vulnerable to infections. The oral thrombopoietin receptor agonist eltrombopag has been tested in patients with chronic hepatitis C and liver cirrhosis (McHutchinson 2007). Eltrombopag increased platelet levels in 75-95% of patients depending on the dose, and antiviral therapy was then initiated. It remains unapproved for this indication.

Neutropenia is another common reason for dose modification. Granulocyte macrophage colony-stimulating factor and granulocyte colony-stimulating factor could be used to stabilize neutrophil counts during IFN therapy (Shiffman 1998, Van Thiel 1997, Younossi 2008). However cost-benefit analyses and further trials are required to establish routine use of these agents.

Flu-like symptoms usually occur during the first weeks of treatment and severity declines over time. These symptoms include fever, chills, headache, arthralgia, and myalgia (Chapter 6, Table 7). Antipyretic drugs such as paracetamol can help to prevent or reduce these side effects.

Neuropsychiatric side effects such as irritability, severe fatigue, and apathy are also frequent and pose a great problem for many patients and their family members. When severe, side effects may reduce adherence to therapy and may result in dose modifications resulting in suboptimal responses. Severe depression can occur and suicide has been reported (Manns 2006). Psychiatric care and the use of antidepressants, especially selective serotonin reuptake inhibitors (SSRIs) are highly effective in HCV patients during IFN-based therapies, when starting early after the onset of clinically relevant depression (Schaefer 2005, Krauss 2008).

IFN has immunomodulatory properties, and treatment can induce autoimmune phenomena (Wesche 2001). This may not be reversible on stopping therapy (Lisker-Melman 1992). Other

autoimmune diseases can be aggravated by IFN therapy (e.g., diabetes or autoimmune hepatitis). LKM antibody-positive individuals require careful monitoring if IFN is considered as treatment. However, IFN therapy seems safe in most HCV/anti-LKM-1-positive patients (Todros 1995).

Table 4.3 – Common side effects (>20% of patients) recorded in the major PEG-IFN/ribavirin trials.*

Side effects	Incidence with PEG-IFN α and ribavirin (Reddy 2007, Zeuzem 2009)
Headache	47-62%
Pyrexia	40-46%
Myalgia	37-56%
Rigor	24-48%
Arthralgia	24-34%
Nausea	35-43%
Loss of appetite	21%
Weight loss	29%
Diarrhea	22%
Alopecia	21-36%
Rash/Dermatitis	20-24%
Injection site inflammation	25%
Pruritus	25-29%
Dyspnea	26%
Fatigue	48-64%
Insomnia	33-40%
Irritability	24-35%
Depression	22-31%

* It is difficult to compare side effects between studies because of significant differences in genetic and socioeconomic backgrounds, methodological differences in side effect assessment, and study inclusion and exclusion criteria. Normal TSH levels pretreatment were a prerequisite.

Ribavirin

The main side effect of ribavirin is haemolytic anaemia that frequently results in ribavirin dose reduction or even discontinuation, especially in patients with HCV genotype 1 (Reddy 2007). Treatment with erythropoietin can effectively reverse ribavirin-associated anaemia, improving quality of life and allowing for easier adherence to ribavirin (Afdahl 2004). However, no difference in SVR was seen in these trials and erythropoietin is off-label in many countries. See Chapter 6 for more on adverse events.

Special populations

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. Treatment indication should not be based on ALT values (Sarrazin 2010). Patients with normal ALT who present with significant liver fibrosis do need an effective treatment. PEG-IFN α plus ribavirin has been shown to be successful (Zeuzem 2004b); the efficacy and tolerability seem to be comparable to that seen in patients with elevated ALT levels.

HCV and liver transplantation

HCV re-infection occurs in almost all patients after liver transplantation. As HCV takes a more rapid course post-transplant than in immunocompetent individuals, treatment needs are obvious. Antiviral therapy started before transplant can prevent re-infection of the graft in two-thirds of patients (Forns 2003); however, treatment is poorly tolerated in those with decompensated cirrhosis (Everson 2004).

In patients with established recurrent hepatitis C, PEG-IFN plus ribavirin led to an initial virological response rate of up to 55% (Dumortier 2004). Ideally, treatment duration should be at least similar to non-transplanted patients although bone marrow toxicity, depression, and rejection are limiting factors (Neff 2004, Rodriguez Luna 2004). With renal insufficiency the ribavirin dose may have to be adjusted. Drop-out rates are high.

Dialysis patients

Before kidney transplantation, HCV should be eliminated. 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 has been contraindicated in this setting. Ribavirin can be given at lower doses in dialysis patients, usually between 200-400 mg daily (Bruchfeld 2001). PEG-IFN α-2a is eliminated mainly by the liver while PEG-IFN α-2b is cleared via the kidney (Cornberg 2002). Thus, only PEG-IFN α-2a is approved in this setting.

Retreatment

Treatment of patients with prior antiviral treatment failure

Treatment failure is 1) the failure to clear HCV RNA at any point during treatment (non-response); 2) recurrent viremia after initial attainment of HCV RNA negativity while treatment is ongoing (breakthrough); or 3) recurrent viremia after attaining HCV RNA negativity at the end of therapy (relapse). As more patients are treated, the size of the patient population who fail to achieve SVR continues to expand. Consequently, retreatment is one of the most important topics in the management of chronic hepatitis C.

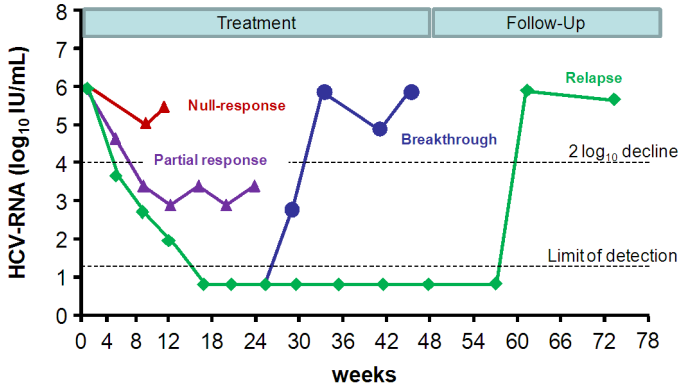

Figure 4.3 – **Treatment failure to antiviral therapy in chronic hepatitis C.** Different scenarios.

In recent clinical trials, a non-response was generally defined as failure to achieve a ≥2 log reduction in HCV RNA by 12 weeks. Classifications of non-response include null-response, which is used as a less than 2 log decline in HCV RNA at any time. A partial virologic response is defined as a ≥2 log decline in HCV RNA during therapy without clearing HCV RNA after 24 weeks of therapy.

Retreatment of patients with relapse after standard therapy

Patients who relapse after IFN-based or PEG-IFN-based combination therapy with ribavirin and who are considered for retreatment should be treated with PEG-IFN/ribavirin at least 48 weeks, independent of the genotype. Strict adherence is paramount to treatment success. A sustained viral response is achieved by 32-50% patients (Appendix, Table 11.7). Patients with HCV genotype 1 and higher fibrosis scores are less likely to achieve an SVR (Poynard 2009, Jacobson 2005). Patients who do not achieve HCV RNA negativity at week 12 have only a 5% chance of achieving SVR.

Retreatment of non-responders to standard therapy

Patients who are non-responders to standard PEG-IFN/ribavirin combination therapy demonstrate SVRs ranging between 2-12% with a standard PEG-IFN/ribavirin re-treatment (Appendix, Table 11.8) (Poynard 2009, Jacobson 2005, Shiffman 2004, Schiff 2008, Marcellin 2008). Thus, indication for retreatment is limited. Retreatment is justified if adherence was a major problem during the previous treatment regimen. Patients with previous partial response may benefit from retreatment with optimized treatment regimen, i.e., extended treatment duration.

If a patient is a previous non-responder to IFN-based or PEG-IFN-based combination therapy and has detectable HCV RNA at Week 12, treatment should be discontinued. If a previous non-responder has undetectable HCV RNA by Week 12, treatment can be continued with a significant chance of SVR. Treatment duration of 72 weeks should be considered. A multivariate analysis in the REPEAT study of critical predictors of response identified a treatment duration of 72 weeks vs 48 weeks as the best predictor of response in this trial. Induction therapy did not result in a significant difference (Marcelin 2008) (Appendix, Table 11.8), confirming previous data (Cornberg 2006).

PEG-IFN maintenance therapy

There are two major trials that have analyzed if maintenance treatment with IFN may alter the natural course of chronic hepatitis C. The authors of the COPILOT study saw no significant difference in the arms although maintenance therapy may have a role in patients with portal hypertension.

In the HALT-C trial, while there were greater reductions in viremia, decrease in alanine aminotransferase and necroinflammation in patients who received PEG-IFN, none of the important clinical outcomes (rates of death, decompensation, hepatocellular carcinoma, and increase in fibrosis) were favorably affected by PEG-IFN therapy (Di Bisceglie 2008). Long-term treatment with low-dose PEG-IFN cannot be recommended for nonresponder patients.

Treatment of Acute Hepatitis C

The goal of acute hepatitis C treatment is the prevention of persistent HCV infection which develops in 50-90% of infected individuals. Two different patient groups require different approaches. The first group, asymptomatic patients, have a high risk for evolution to a chronic state and should probably be treated immediately; unfortunately, most patients will never be treated, as asymptomatic HCV infections typically go unnoticed.

The second group, patients with symptomatic acute HCV infection, are more likely to clear HCV spontaneously (Gerlach 2003), usually within the first 12 weeks after onset of symptoms. In order to avoid unnecessary treatment, it might be preferable to postpone treatment and identify those patients who clear the infection. Those who are still HCV RNA positive 12 weeks after the onset of symptoms should receive treatment. Postponed treatment resulted in a sustained virological response (self-limited and treatment-induced) in 91% of patients (Gerlach 2003).

The treatment of choice of acute hepatitis C infection is recombinant interferon-α or peginterferon-α (PEG-IFN-α) monotherapy for 24 weeks. This regimen prevents the development of chronic hepatitis C in approximately 90% of patients with good adherence (Jaeckel 2001, Wiegand 2006,

Wiegand 2006; see Appendix, Table 11.1); coadministration with ribavirin does not seem to be necessary. The imminent approval of protease inhibitors and polymerase inhibitors is expected to offer additional treatment options. These highly effective antiviral drugs have fewer side effects and may allow for short-term treatment of all patients with acute HCV infection.

Outlook

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

Further progress is looming on the horizon. Knowledge of the molecular structure of the hepatitis C proteins has allowed the design of new drugs targeting the sites of HCV-encoded enzymes that are important for the replication of the virus. The HCV protease and the HCV polymerase are currently the main targets (see the detailed discussion in the following chapter). Approval of the first protease inhibitors telaprevir and boceprevir is due in 2011. Even if PEG-IFN and ribavirin remain the backbone of standard therapy for the next years, the new drugs have the potential of transforming the treatment of chronic hepatitis C infection. Further improvements may be “just around the corner”.

5. New Agents for Treating Hepatitis C

Christian Lange and Christoph Sarrazin

From the introduction of interferon (IFN) α monotherapy to the current standard of care, combination therapy with pegylated interferon α plus ribavirin, the ability of achieving a sustained virologic response (SVR), defined by undetectable HCV RNA 24 weeks after treatment completion, has improved significantly (Zeuzem 2009). However, more than half of all patients with chronic HCV genotypes 1 or 4 still do not achieve SVR, contrasting with rates of approximately 70-90% in those infected with HCV genotypes 2 or 3. In addition, treatment with standard of care is long (up to 72 weeks), has numerous side effects leading to early discontinuation in up to 20% of patients, and interferon α is contraindicated in a significant proportion of patients due to concomitant diseases and other circumstances (Zeuzem 2009).

The exploding knowledge of the HCV life cycle and structural features of HCV proteins, obtained by replicative cell culture systems and crystallographic analyses, has spurred the development of many promising direct-acting antiviral agents (DAA), previously known as "specifically targeted antiviral therapy for hepatitis C" (STAT-C) compounds (Kim 1996, Lindenbach 2005, Lohmann 1999, Moradpour 2007, Wakita 2005).

In principle, each of the four HCV structural and six non-structural proteins, HCV-specific RNA structures such as the IRES, as well as host factors on which HCV depends, are suitable targets for DAA agents. In the following section, DAA compounds currently in clinical development are presented (Figure 5.1).

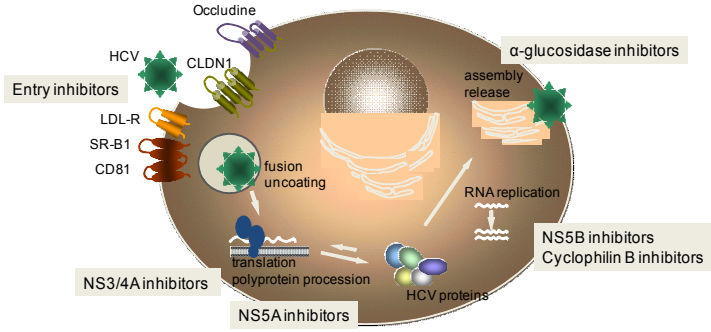

Figure 5.1 – HCV life cycle and targets for directly acting antiviral agents (DAAs).

Compounds targeting HCV polyprotein processing

NS3-4A protease inhibitors

HCV NS3-4A is a non-covalent complex made of the NS3 protein and its cofactor polypeptide NS4A. NS3 is a 70 kD multifunctional protein, with a serine protease domain located in the N terminal one-third (amino acid [aa] 1-180) and an RNA helicase/NTPase domain in the C terminal two-thirds (aa 181-631) (Figure 5.2). The serine protease domain comprises two β barrels and four α helices. The serine protease catalytic triad – histidine 57, asparagine 81 and serine 139 – is located in a small groove between the two β barrels (Kim 1996, Kim 1998). The NS3-4A protease cleaves the junctions between NS3/NS4A, NS4A/NS4B, NS4B/NS5A and NS5A/NS5B. Besides its essential role in protein processing, NS3 is integrated into the HCV RNA

replication complex, supporting the unwinding of viral RNA by its helicase activity. Moreover, NS3 might play an important role in HCV persistence by inhibiting innate immune mechanisms via blocking of RIG-I and toll-like receptor- (TRIF, Cardif) and subsequently interferon-signaling pathways (Meylan 2005). Thus, NS3 inhibition might support viral clearance by restoring the innate immune response.

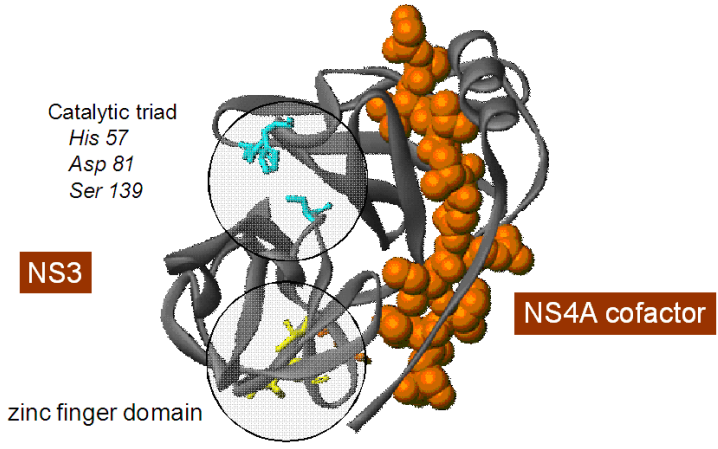

Figure 5.2 – Molecular structure of the HCV NS3-4A protease.

The location of the active site of the NS3-4A in a shallow groove makes the design of compound inhibitors relatively difficult. Nevertheless, many NS3-4A protease inhibitors are in development and can be divided into two classes, macrocyclic inhibitors and linear tetra-peptide α-ketoamid derivatives. In general, NS3-4A protease inhibitors have been shown to strongly inhibit HCV replication during monotherapy, but also may cause the selection of resistant mutants, which is followed by viral breakthrough. The additional administration of pegylated interferon and ribavirin, however, was shown to reduce the

frequency of development of resistance. The most advanced NS3-4A inhibitors are telaprevir and boceprevir, which are expected to be approved in 2011/12.

Telaprevir (VX-950)

Telaprevir is an orally bioavailable, peptidomimetic NS3-4A protease inhibitor. Telaprevir is an α-ketoamid derivative binding the enzyme covalently but reversibly, with a half-life of 58 minutes of the enzyme-inhibitor complex (Lin 2006) (Figure 5.3).

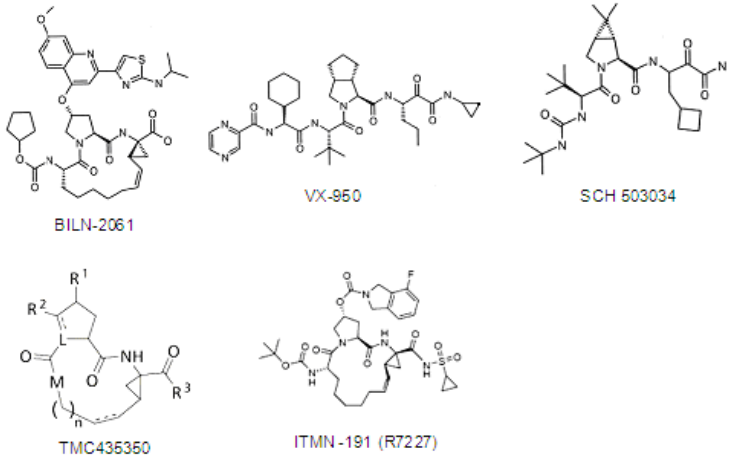

Figure 5.3 – Molecular structure of selected NS3-4A inhibitors.

Phase I and II studies. In a first phase 1 trial in HCV genotype 1 patients, antiviral activity, safety, optimal dosage, and pharmacokinetics of telaprevir monotherapy were assessed. Telaprevir over 14 days led to a rapid decline of HCV RNA serum levels (Reesink 2006). The best results were obtained with 750 mg telaprevir q8h with a median reduction of HCV RNA of 4.4 $\log_{10}$ after 14 days of treatment, which became the basis for telaprevir

dosage in most of the following clinical trials. Viral rebound due to selected mutants occurred in all patients after treatment completion and in some patients even during monotherapy treatment (Sarrazin 2007a). Subsequent phase I studies have shown that the addition of pegylated interferon α with or without ribavirin leads to an even more pronounced HCV RNA decline, and reduces the frequency of resistant mutants and viral breakthrough with telapravir (Forestier 2007, Lawitz 2008).

Larger phase II clinical trials showed that telaprevir can significantly enhance SVR rates in treatment-naive HCV genotype 1 patients (PROVE 1 and 2 trial) and in treatment-experienced patients (PROVE 3 trial) when used with pegylated interferon α and ribavirin.

In PROVE 1 and 2, telaprevir plus PEG-IFN α-2a with or without ribavirin were administered for 12 weeks, followed by PEG-IFN α-2a and ribavirin alone for 0 to 36 weeks (Hezode 2009, McHutchison 2009). SVR rates ranged from 35% to 69%, compared to 41-46% after standard treatment. Thus, 24 to 48 weeks of total therapy including 12 weeks of telaprevir-based triple therapy greatly improved SVR rates in treatment-naïve HCV genotype 1 patients compared to standard of care. However, relapse rates of 30% after 12 weeks of therapy indicate that short treatment duration is not sufficient for HCV genotype 1 patients in general. Since preliminary data show that some predictors of virologic response to conventional therapy such as early on-treatment viral kinetics or genetic polymorphisms near the IL28B gene are predictive for telaprevir-based therapies, future studies may help in defining parameters to select patients who qualify for shorter treatment durations (Akuta 2010). In PROVE 2 a ribavirin-free treatment arm was included. SVR rates after 12 weeks of telaprevir, PEG-IFN α-2a with (60%) or without (36%) ribavirin highlight the importance of ribavirin in telaprevir-based regimens.

The PROVE 3 trial showed that telaprevir-based triple therapy also greatly improved SVR rates in HCV genotype 1 relapsers (69-76%) and non-responders (38-39%), compared to retreatment with standard of care (14%) (McHutchison 2010). As in the PROVE 1 and 2 studies, viral breakthrough was observed more frequently in patients infected with genotype 1a than in patients infected with genotype 1b. Nevertheless, the results of PROVE 3 indicate that STAT-C compounds have an enormous potency in prior non-responders and relapsers to standard treatment.

Telaprevir and different HCV genotypes. Telaprevir alone or in combination with PEG-IFN and ribavirin was less effective in treatment-naïve patients infected with other genotypes. For HCV genotype 2 a somewhat weaker antiviral activity in comparison with genotype 1 with a mean viral decline of 3.9 $\log_{10}$ IU/ml over 14 days monotherapy was observed; in genotype 3 and 4 patients no significant antiviral activity was detectable (0.5-0.9 $\log_{10}$ decline) (Benhamou 2010, Foster 2010).

Telaprevir phase III studies. The ADVANCE trial enrolled more than 1000 treatment-naïve HCV genotype 1 patients to evaluate 24 and 48 weeks of telaprevir-based therapy (Jacobson 2010). Telaprevir was dosed at 750 mg every 8 hours and given for 8 or 12 weeks in combination with PEG-IFN α-2a and ribavirin followed by PEG-IFN α-2a and ribavirin alone until treatment week 24 or 48. A response-guided approach was applied to define the overall treatment period. Patients with or without an extended rapid virologic response (eRVR, undetectable HCV RNA at treatment weeks 4 and 12) received 24 or 48 weeks of total therapy, respectively. The novel concept of eRVR was introduced in order to identify patients with viral breakthrough of telaprevir resistant variants, which may occur after achieving RVR according to the traditional definition. SVR rates in the ADVANCE trial were 69% and 75% for 8 and 12 weeks triple therapy followed by 24 or 48 weeks of total treatment (response

guided according to eRVR), compared to 44% after standard treatment, and eRVR rates were 58% (Figure 5.4a).

In the ILLUMINATE trial telaprevir was given for 12 weeks in combination with PEG-IFN α-2a and ribavirin followed by PEG-IFN α-2a and ribavirin alone until treatment week 24 or 48, independent of whether eRVR was achieved or not (Sherman 2010). Importantly, 48 weeks of total treatment were not superior to 24 weeks in patients with eRVR (88 and 92%, respectively).

The phase III REALIZE study enrolled more than 650 patients with prior failure to standard treatment (Figure 5.4a) (Vertex Pharmaceuticals 2010). PEG-IFN α-2a and ribavirin were given for 48 weeks including 12 weeks of telaprevir at a dose of 750 mg every eight hours. In one treatment arm, telaprevir was initiated after a 4 week lead-in phase of PEG-IFN α-2a and ribavirin alone. SVR rates were 86%, 57%, and 31% in relapsers, partial non-responders, and null-responders to prior treatment, respectively, compared to 24%, 15%, and 5% after standard treatment, respectively. SVR rates were not improved by the lead-in phase, but the lead-in approach may help to identify patients with a poor chance of cure even with triple therapy. Viral breakthrough of resistant variants occurred in up to 25% of all treatment-experienced patients, compared to 1-5% of treatment-naïve patients. Nevertheless, the REALIZE study confirmed the high potential of telaprevir-based triple therapy in treatment-experienced patients.

Tolerability of telaprevir. In the PROVE trials, serious adverse effects led to premature treatment termination in up to 18% of all subjects treated with telaprevir in contrast to 4% of patients with standard therapy (Hezode 2009, McHutchison 2009). The most important side effects of telaprevir are rash, gastrointestinal disorders and anaemia.

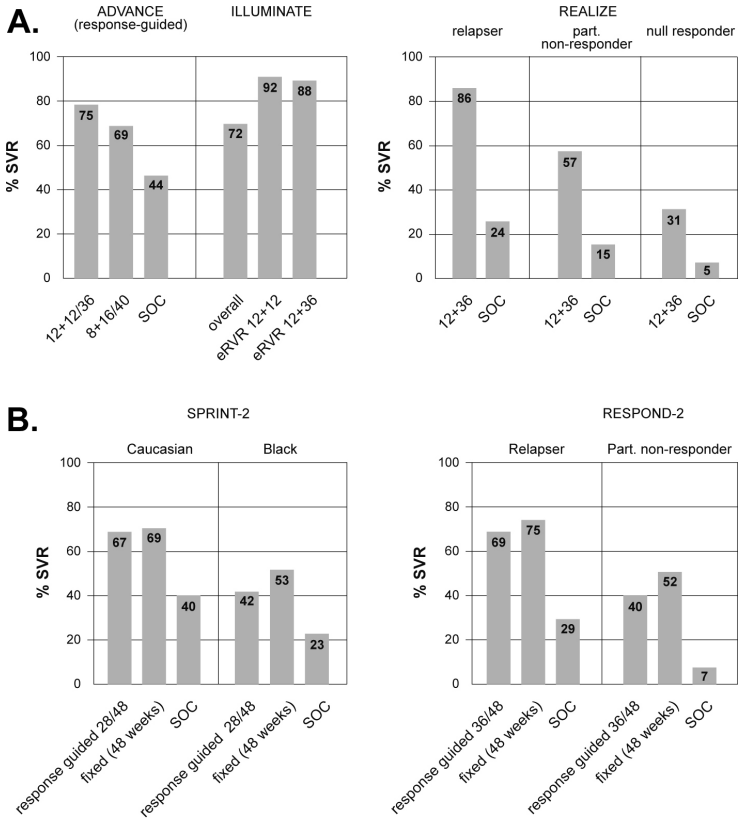

Figure 5.4 – SVR rates in phase III clinical trials evaluating telaprevir (A) or boceprevir (B) in combination with PEG-IFN α and ribavirin. ADVANCE, ILLUMINATE and SPRINT-2 enrolled treatment-naive patients, REALIZE and RESPOND-2 enrolled treatment-experienced patients. Telaprevir was administered for 8 or 12 weeks in combination with PEG-IFN α-2a and ribavirin, followed by 12-40 weeks of PEG-IFN α-2a and ribavirin alone. Boceprevir was administered over the whole treatment period of 28 or 48 weeks in combination with PEG-INF α-2b and ribavirin, except for the first 4 weeks of lead-in therapy. eRVR, extended early virologic response; SOC, standard of care; LI, lead-in (4 weeks of PEG-INF α plus ribavirin only).

Treatment discontinuation rates in the phase III studies (5-8%) suggest that an improved management of these side effects can avoid treatment discontinuation in most cases, but the triple-therapy approach implies an additional burden for patients in tolerability and adherence.

Boceprevir (SCH 503034)

Boceprevir is another novel peptidomimetic orally bioavailable α-ketoamid HCV protease inhibitor that forms a covalent but reversible complex with the NS3 protein (Malcolm 2006) (Figure 5.3).

Boceprevir phase I and II studies. The antiviral activity of boceprevir (100 to 400 mg daily) monotherapy was somewhat weaker than that of telaprevir with mean maximum reductions in HCV RNA load of up to 2.06 $\log_{10}$ (Sarrazin 2007b), and viral breakthrough with resistant variants was observed in a significant number of patients (Susser 2009). A subsequent phase Ib study evaluated the combination of boceprevir and PEG-IFN α-2b in genotype 1-infected non-responders to standard therapy, which resulted in a larger HCV RNA decline and lower rates of viral breakthrough (Sarrazin 2007b).

A phase II clinical trial (SPRINT 1 study) investigated safety, tolerability and antiviral efficacy of boceprevir at a higher dosage than in the phase I trials (800 mg three times a day) in combination with PEG-IFN α-2b and ribavirin in treatment-naïve HCV genotype 1 patients (Kwo 2010). Treatment with boceprevir in combination with PEG-IFN α-2b and ribavirin was either continuous for 28 or 48 weeks or for 24 or 44 weeks after a previous 4-week treatment period with PEG-IFN α-2b and ribavirin alone (the lead-in). This lead-in design was chosen to determine whether pretreatment with PEG-IFN α-2 and ribavirin has beneficial effects in avoiding the development of resistance and on antiviral efficacy. SVR rates after continuous treatment vs. treat-

ment with lead-in were 54% vs 56% and 67% vs 75% after 28 and 48 weeks of total therapy. The most common side effects related to boceprevir were anaemia, nausea, vomiting and dysgeusia. In general, SPRINT-1 revealed a higher antiviral efficacy with boceprevir in comparison to the standard of care alone (38% SVR) with slightly better results in the lead-in arms, especially for the longer treatment duration of 48 weeks. However, with 38% RVR rates boceprevir triple therapy seems to be less potent than with telaprevir triple therapy (~70%).

Boceprevir phase III studies. The phase III SPRINT-2 clinical trial evaluated boceprevir in more than 1000 treatment-naïve patients (Figure 5.4b). Equivalent to the SPRINT-1 study design, patients received 800 mg boceprevir three times daily in combination with PEG-IFN α-2b and weight based ribavirin for 24 or 44 weeks, after a four week lead-in phase of PEG-IFN α-2b plus ribavirin (Poordad 2010). Patients who were randomized to the 24-week triple therapy arm received an additional 24 weeks of PEG-IFN α-2b and ribavirin only if they tested positive for HCV RNA between weeks 8 and 24 of triple therapy (definition of non-eRVR for boceprevir response-guided approach). SVR rates in caucasians were 67% and 68% compared to 40% in the control group, but somewhat lower in blacks (53%, 42%, 23%, respectively). In patients with eRVR (47%) SVR rates were similarly high in those treated for 28 weeks (97%) and those treated for 48 weeks (96%).

RESPOND-2 evaluated boceprevir in combination with PEG-IFN α-2b and ribavirin for 36 and 48 weeks in relapsers and partial non-responders to previous standard treatment (Figure 5.4b) (Bacon 2010a). All investigational arms started with a lead-in strategy of PEG-IFN α-2b and ribavirin. Shortened treatment duration of 36 weeks was limited to patients who were HCV RNA negative at week 8 (46% of patients). SVR rates in relapsers and partial null-responders to previous treatment were 69-75% and

40-52%, respectively, compared to 29% and 7% after standard treatment. As SVR rates of patients with HCV RNA negativity at week 8 treated for 36 and 48 weeks were statistically not different (86% and 88%, respectively), a response-guided treatment approach with boceprevir seems possible also for relapsers and partial non-responders.

Tolerability of boceprevir. The most frequent side effects of boceprevir were anaemia and dysgeusia. In SPRINT-1, anaemia was associated with increased SVR rates (Kwo 2010). However, epoetin α had to be used in 40% of all boceprevir-treated patients.

Ciluprevir (BILN 2061)

The first clinically tested NS3-4A inhibitor was ciluprevir (BILN 2061), an orally bioavailable, peptidomimetic, macrocyclic drug binding non-covalently to the active center of the enzyme (Lamarre 2003) (Figure 5.3). Ciluprevir monotherapy was evaluated in a double-blind, placebo-controlled pilot study in treatment-naïve genotype 1 patients with liver fibrosis and compensated liver cirrhosis (Hinrichsen 2004). Ciluprevir was administered twice daily for two days at a range of doses and led to a mean 2-3 $\log_{10}$ decrease of HCV RNA serum levels in most patients. Importantly, the stage of disease did not affect the antiviral efficacy of ciluprevir. The tolerability and efficacy of ciluprevir in genotype 2- and 3-infected individuals was then examined in an equivalent study design, where ciluprevir's activity was less pronounced and more variable (Reiser 2005).

Although the development of ciluprevir was stopped because of serious cardiotoxicity in an animal model, it provided the proof-of-principle for successful suppression of HCV replication by NS3-4A inhibitors in patients with chronic hepatitis C.

Other NS3-4A protease inhibitors

Other NS3 protease inhibitors are currently in phase 1-2 development (danoprevir (R7227/ITMN191), vaniprevir (MK7009), BI201335, TMC435, narlaprevir (SCH900518), BMS-650032, PHX1766, ACH-1625, IDX320, ABT-450, MK-5172, GS-9256, GS-9451). Comparable antiviral activities to telaprevir and boceprevir in HCV genotype 1 infected patients have been observed, and triple therapy studies for a number of compounds have been initiated (Brainard 2010, Reesink 2010, Sarrazin 2010). Potential advantages of these second- and third-generation protease inhibitors might be improved tolerability, broader genotypic activity, different resistance profiles, and/or improved pharmacokinetics to allow for once-daily dosage (e.g., TMC435). Different resistance profiles between linear tetrapeptide and macrocyclic inhibitors binding to the active site of the NS3 protease have been noted. However, R155 is the main overlapping position for resistance and different mutations at this amino acid site within the NS3 protease confer resistance to nearly all protease inhibitors which are currently in advanced clinical development (Sarrazin 2010). An exception is MK-5172, which exhibits potent antiviral activity against variants carrying mutations at position R155. In addition, MK-5172 had potent antiviral activity against both HCV genotype 1 and 3 isolates (Brainard 2010).

Resistance to NS3-4A protease 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 (direct acting agents) compounds can develop. During treatment with specific antivirals, these preexisting drug-resistant variants have a fit-

ness 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 2007a, Sarrazin 2010, Tong 2006). Nevertheless, HCV quasispecies resistant to NS3-4A protease inhibitors or non-nucleoside polymerase inhibitors can be detected at low levels in some patients who were never treated with specific antivirals before (Gaudieri 2009, Kuntzen 2008). The clinical relevance of these pre-existing mutants is not completely understood, although there is evidence that they may reduce the chances of achieving an SVR after treatment with DAA compounds.

Table 5.1 – Resistance mutations to HCV NS3 protease inhibitors.

	36	54	55	60	155	156A	156B	168	170
Telaprevir (linear)			*						
Boceprevir (linear)									
SCH900518 (linear)									
BILN-2061 ** (macrocyclic)									
R7227/ITMN191 (macrocyclic)						*	*		
MK-7009 (macrocyclic)									
TMC435 (macrocyclic)									
BI-201335 (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 vitro* but not described in patients

Table 5.1 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 which are currently in advanced clinical development (Sarrazin 2010). Importantly, many resistance mutations could be detected *in vivo* only by clonal sequencing. For example, mutations at four positions conferring telaprevir resistance have been characterized so far (V36A/M/L, T54A, R155K/M/S/T and A156S/T), but only A156 could be identified initially *in vitro* in the replicon system (Lin 2005, Sarrazin 2007a). 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. 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 and ribavirin, viral resistance and breakthrough occurs 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).

Compounds Targeting HCV Replication

NS5B polymerase inhibitors

The HCV NS5B protein is an RNA-dependent RNA polymerase. NS5B catalyzes the synthesis of a complementary negative-strand RNA by using the positive-strand RNA genome as a template, and subsequently catalyses genomic positive-strand RNAs from these negative-strand RNA templates (Bartenschlager 2004, Lesburg 1999) (Figure 5.5).

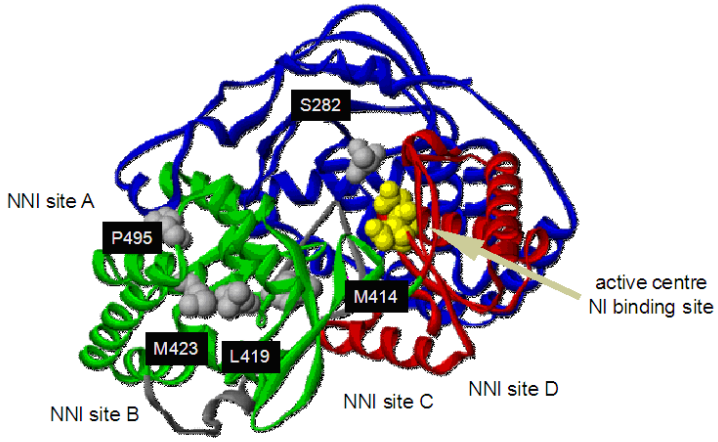

Figure 5.5 – Structure of the HCV NS5B RNA polymerase and binding sites.

NS5B RNA polymerase inhibitors can be divided into two distinct categories. Nucleoside analogue inhibitors (NIs) like valopicitabine (NM283), Mericitabine (R7128), R1626, PSI-7851 or IDX184 mimic the natural substrates of the polymerase and are incorporated into the growing RNA chain, thus causing direct chain termination by tackling the active site of NS5B (Koch 2007). 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 genetic barrier in the development of resistances to NIs.

In contrast to NIs, the heterogeneous class of non-nucleoside inhibitors (NNIs) achieves NS5B inhibition by binding to different allosteric enzyme sites, which results in conformational protein change before the elongation complex is formed (Beaulieu 2007). For allosteric NS5B inhibition high chemical affinity is required. NS5B is structurally organized in a characteristic "right hand motif", containing finger, palm and thumb domains, and offers at least four NNI-binding sites, a benzimidazole-(thumb 1)-, thiophene-(thumb 2)-, benzothiadiazine-(palm 1)- and benzofuran-(palm 2)-binding site (Beaulieu 2007, Lesburg 1999) (Figure 5.5). Because of their distinct binding sites, different polymerase inhibitors can theoretically be used in combination or in sequence to manage the development of resistance. Because NNIs bind distantly to the active centre of NS5B, their application may rapidly lead to the development of resistant mutants *in vitro* and *in vivo*. Moreover, mutations at the NNI binding sites do not necessarily lead to impaired function of the enzyme. Figure 5.6 shows the structure of selected nucleoside and non-nucleoside inhibitors.

Nucleoside analogues

Mericitabine (R7128) is the most advanced nucleoside polymerase inhibitor. Interim results of current phase 2 clinical trials in HCV genotype 1-, 2- and 3-infected patients of Mericitabine in combination with PEG-IFN and ribavirin revealed high early virologic response rates (>80%) (Jensen 2010). In an all-oral regimen, administration of Mericitabine in combination with the protease inhibitor R7227/ITMN191 for 14 days, a syner-

gistic antiviral activity of both drugs was observed (Gane 2010). Also from these studies no viral breakthrough with selection of resistant variants was reported.

Other nucleoside analogues (e.g., PSI-7851 and IDX184) are in earlier stages of clinical development (Sarrazin 2010).

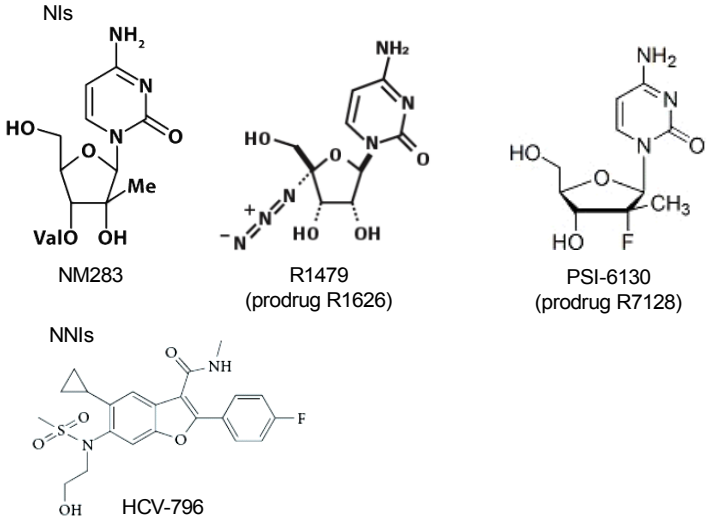

Figure 5.6 – Molecular structure of selected NS5B polymerase inhibitors.

Valopicitabine and R1626 drugs are no longer being developed. Valopicitabine (NM283, 2'-C-methylcytidine/NM107), the first nucleoside inhibitor investigated in patients with chronic hepatitis C, showed a low antiviral activity (Afdhal 2007). Due to gastrointestinal side effects the clinical development of NM283 was stopped.

The second nucleoside inhibitor reported in patients with chronic hepatitis C was R1626 (4'-azidocytidine/PSI-6130). A phase 1 study in genotype 1 infected patients observed a high

antiviral activity at high doses of R1626 in genotype 1 infected patients (Pockros 2008a). No viral breakthrough with resistant variants was reported from monotherapy or combination studies with PEG-IFN ± ribavirin (Pockros 2008b). Due to severe lymphopaenia and infectious disease adverse events, development of R1626 was halted.

Non-nucleoside analogues

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., NNI site 1 inhibitor BI207127; NNI site 2 inhibitors filibuvir (PF-00868554), VCH-759, VCH-916 and VCH-222; NNI site 3 inhibitor ANA598, NNI site 4 inhibitors HCV-796, GS-9190 and ABT-333) (Ali 2008, Cooper 2007, Erhardt 2009, Kneteman 2009, Sarrazin 2010). In general, these non-nucleoside analogues display a low to medium antiviral activity and a low genetic barrier to resistance, evidenced by frequent viral breakthrough during monotherapy studies. In contrast to the broad activity of nucleoside-analogues against various HCV genotypes, non-nucleoside analogues in general are only effective against individual HCV genotypes (Sarrazin 2010).

The impact of non-nucleoside inhibitors on SVR in combination with PEG-IFN α and ribavirin remains to be elucidated.

NS5A inhibitor

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 to-

gether 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, for example, has been associated with interferon resistance (Wohnsland 2007). Furthermore, mutations within the NS5A protein have been clinically associated with resistance / sensitivity to IFN-based antiviral therapy (Wohnsland 2007).

BMS-790052 was the first NS5A inhibitor to be evaluated clinically. BMS-790052 monotherapy leads to a sharp initial decline of HCV RNA concentrations, though its genetic barrier to resistance is relatively low (Gao 2010). According to an interim analysis, treatment with BMS-790052 in combination with PEG-IFN α and ribavirin results in RVR and cEVR rates in over 80% of patients. Importantly, BMS-790052 displays a high antiviral activity against most HCV genotypes.

Combination therapies of specific antivirals

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

mens, including NS3 protease inhibitors, nucleoside and non-nucleoside NS5B inhibitors, NS5A inhibitors, and ribavirin. Recent interim analyses indicate that most patients treated with only two DAA agents experience viral breakthrough, which can be significantly reduced by the addition of ribavirin without PEG-IFN α (Zeuzem 2010a).

Host proteins as targets in treating hepatitis C

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 folding and function of many proteins. Cyclophilin B enhances HCV replication by incompletely understood mechanisms, which include modulation of NS5B activity. Debio-025 (alisporivir) is an orally bioavailable cyclophilin B inhibitor exerting an antiviral impact on both HCV and HIV replication. In clinical trials in HIV/HCV-coinfected patients, treatment with 1200 mg Debio-025 twice daily for two weeks led to a mean $\log_{10}$ reduction of HCV RNA of 3.6 and of HIV DNA of 1.0 (Flisiak 2008). Debio-025 was well tolerated and no viral breakthrough occurred during the 14 days of treatment.

Combination therapy of Debio-025 200 mg, 600 mg or 1000 mg and PEG-IFN α-2a was evaluated in a double-blind placebo-controlled phase II trial in treatment-naïve patients monoinfected with HCV genotypes 1, 2, 3 or 4. Treatment was performed for 29 days. Mean $\log_{10}$ reductions in HCV RNA at day 29 were 4.75 (1000 mg), 4.61 (600 mg) and 1.8 (200 mg) in the combination therapy groups compared to 2.49 (PEG-IFN α-2a alone) and 2.2 (1000 mg Debio-025 alone) in the monotherapy groups. No differences in antiviral activity were observed between individuals infected with different genotypes. Debio-025 was safe and well tol-

erated but led to a reversible bilirubin increase in some of the patients treated with 1000 mg Debio-025 daily (Flisiak 2009). A high genetic barrier to resistance of Debio-025 and a broad HCV genotypic activity highlight the potential of drugs targeting host proteins. Studies determining SVR rates of combination therapy with Debio-025 and PEG-IFN α-2a are ongoing.

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 2 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 (Bacon 2010b, Rossignol 2009). Additional studies are warranted to determine the role of nitazoxanide in the treatment of chronic hepatitis C.

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 lead to a decline in HCV RNA between 0.55 to 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 of between 1.63 and

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

Novel interferons

In the last few years, attempts have been made to reduce side effects and treatment discomfort of PEG-IFN α. However, interferons with a 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 2010b). Still promising is the development of PEG-IFN lambda (λ)-1. Like other type 3 interferons, IFNλ-1, which is also called interleukin-29 (IL-29), binds to a different receptor than IFN α, but downstream signaling pathways of IFN λ and IFN α are similar. The IFN λ receptor is predominantly expressed in hepatocytes. Thus, interferon-related side effects may be less frequent during PEG-IFN λ treatment. A phase I clinical trial evaluating pegylated interferon λ with or without ribavirin has completed (Muir 2010) and interferon λ was well tolerated and the majority of patients achieved a greater than 2 $\log_{10}$ decline of HCV RNA within 4 weeks.

Outlook

Due to their high potency in achieving SVR, there is no doubt that triple therapy approaches including direct-acting antiviral agents in combination with pegylated interferon α and ribavirin will enrich future treatment options for patients with chronic hepatitis C. Approval of the NS3-4A inhibitors telaprevir and boceprevir in the very near future will give a chance of eradicating HCV in a majority of treatment-naïve HCV genotype 1 patients and in up to 50% of treatment-experienced HCV genotype 1 patients. Nucleoside analogue NS5B inhibitors, NS5A in-

hibitors and agents targeting host proteins such as Debio-025 are highly promising for patients infected with other HCV genotypes. However, additional side effects and costs demand intensive efforts to clearly define patients who require triple treatment or not, and to define optimal treatment schedules for individualized durations of therapy. Moreover, it needs to be clarified whether all oral combinations of direct-acting antiviral agents, with or without ribavirin, are capable of eradicating or continuously suppressing HCV. This would be of interest particularly for patients with contraindications to the current standard of care.

6. Adverse Events and Drug Interactions

Martin Schaefer and Stefan Mauss

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

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

Systemic Symptoms

Flu-like symptoms, fever, arthralgia and myalgia will usually diminish spontaneously during the first weeks of treatment.

Gastrointestinal disorders. Nausea and loss of appetite, dry mouth.

Weight loss in interferon-based studies is around 6-10% over 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 anaemia. In these patients hypothyroidism has to be excluded. Treatment in patients without an underlying complication such as anaemia, depression or hypothyroidism is difficult. For chronic fatigue, currently available data does not point to specific treatment recommendations.

Cough is frequently reported and is most probably due to oedema of the mucosa of the respiratory system. Advanced, not well-controlled asthma bronchiale may be a contraindication for hepatitis C therapy. Dyspnoea 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 commonly emerging IFN α-induced psychiatric adverse events are outlined in Tables 6.1 and 6.2. Most hepatology trials are only monitored for "major depression" without using depression scales, leading to an underreporting of mild to moderate depressive episodes.

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

Although history of major depression or suicide attempts is considered a contraindication for interferon-based therapy, treatment of patients with pre-existing psychiatric disorders can be initiated in close collaboration with an experienced

psychiatrist in a well-controlled setting (Schaefer 2004, Schaefer 2007b).

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

Psychiatric side effects	Incidence
Fatigue	70-80%
Sleep disturbances	46-65%
Irritability	60-85%
Cognitive disturbances with impairment of concentration and memory	45-60%
Depressive episodes	50-60%
- Mild	20-40%
- Moderate	15-30%
- Severe	1-5%
Delirium, psychosis	1-6%
Suicidal syndrome	<1%
Fatigue	70-80%

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

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

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

Current data supports the view that all patients with pre-existing depressive symptoms should receive a prophylactic treatment with antidepressants (Musselman 2001, Capuron 2002, Krauss 2005, Raison 2007). Evidence from larger prospective controlled studies is still needed in order to define if prophylactic antidepressants are useful across the board for all patients.

As sleeping disorders can be a symptom of depression, it is also important to identify existing depressive symptoms and add antidepressants with sedative effects, such as mirtazapine, as needed.

Haematologic and immunologic effects

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

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

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

For boceprevir, anaemia is the most important adverse event requiring dose adjustment of ribavirin or in some cases the use of erythropoietin or red blood cell transfusion in a considerable number of patients. Nausea and diarrhoea are seen frequently in patients on boceprevir. Treatment of skin adverse events is

similar to that for telaprevir-associated skin toxicity (Anonymous 2010).

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

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

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

Telaprevir and Boceprevir

Triple combination therapy of pegylated interferon, ribavirin plus one of the new HCV protease inhibitors telaprevir or boceprevir will become standard of care for the treatment of genotype 1 patients. Efficacy will increase, as will toxicity.

Conclusion

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

The first generation of HCV protease and polymerase inhibitors will be combined with interferon and ribavirin as triple combination therapy to improve efficacy in HCV genotype 1 patients. Current studies indicate that most agents will have a substantial adverse event profile increasing haematological or dermatological problems. Early assessment of and therapy for adverse events may prevent premature treatment discontinuation.

7. Extrahepatic Manifestations

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, haematological, endocrine or dermatological disorders. The pathogenesis of EHM is not fully understood, although most studies suggest that the presence of mixed cryoglobulinaemia (MC), particular lymphotropism of the virus, molecular mimicry and non-cryoglobulinaemic 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
Rheumatic disorders	Mixed cryoglobulinaemia* Cryglobulinaemic vasculitis* Peripheral neuropathy* Membranoproliferative glomerulonephritis (GN)* Membranous GN* Rheumatoid arthralgias/oligo-polyarthritis Rheumatoid factor positivity* Sicca syndrome
Haemotologic disorders	Lymphoproliferative disorders/Non-Hodgkin Lymphomas* Immune thrombocytopaenic purpura (ITP) Monoclonal gammopathies* Autoimmune haemolytic anaemia
Dermatologic disorders	Palpable purpura Porphyria cutanea tarda (PCT) Lichen planus Pruritus
Miscellaneous	Chronic fatigue*, subclinical cognitive impairment, psychomotoric deceleration, symptoms of depression* Myopathy Cardiomyopathy/Myocarditis Idiopathic pulmonal fibrosis

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

Lymphoproliferative Disorders

Cryoglobulinaemia refers to the presence of abnormal immunoglobulins in the serum. Cryoglobulins (CGs) are classified into three types. Type II CG, consisting of monoclonal and/or polyclonal immunoglobulins, are prevalent in patients with chronic HCV infection, while type I CGs, consisting exclusively of monoclonal components, are mostly found in patients with lymphoproliferative disorders. Type II or type III mixed cryoglobulinaemia (MC) are found in 19%-50% of patients but

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

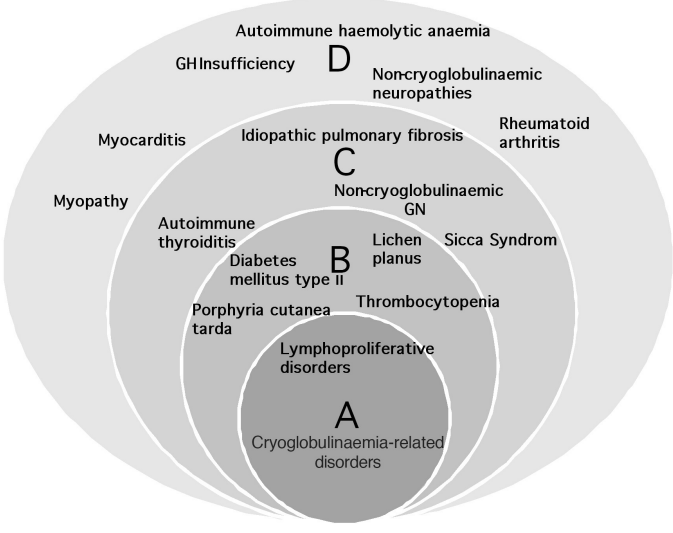

Figure 7.1. Schematic representation of EHM categories (modified after Zignego 2007a). A) Associations with strong epidemiological evidence and clear pathogenetic mechanisms; B) Associations with high prevalence, but unclear pathogenetic mechanisms; C) Associations for which high prevalence in HCV could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

Table 7.2 – Diagnostic criteria of cryoglobulinaemic syndrome.

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

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

Clinical features of mixed cryoglobulinaemia. HCV-related MC proceeds mostly asymptomatically and has no significant influence on the course of chronic liver inflammation. On the other hand, symptomatic mixed cryoglobulinaemia is associated with higher mortality (Ferri 2004). Clinical manifestations of symptomatic mixed cryoglobulinaemia 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 leukaemia/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 cryoglobulinaemia type II evolve into B cell NHL after long-lasting infection. However, a remarkably high prevalence of B cell NHL was also found in HCV patients without mixed cryoglobulinaemia (Silvestri 1997). Genetic predisposition and other factors seem to

have a major impact on the development of LPDs in HCV-positive patients (Matsuo 2004).

Aetiology 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

While asymptomatic **mixed cryoglobulinaemia** *per se* does not constitute an indication for treatment, symptomatic mixed cryoglobulinaemia should always be treated. Because asymptomatic cryoglobulinaemia 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 taken into consideration (Craxi 2008) (Figure 7.2).

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 cryoglobulinaemia-related vasculitis resistant to antiviral therapy

seems to be the optimal therapeutic strategy (Saadoun 2008). In severe rituximab-refractory mixed cryoglobulinaemia-related vasculitis or acute manifestations, cycles of plasma exchange plus corticosteroids and eventually cyclophosphamide are indicated.

Use of IFN α in presence of HCV-related neuropathy requires a cautious risk-benefit assessment.

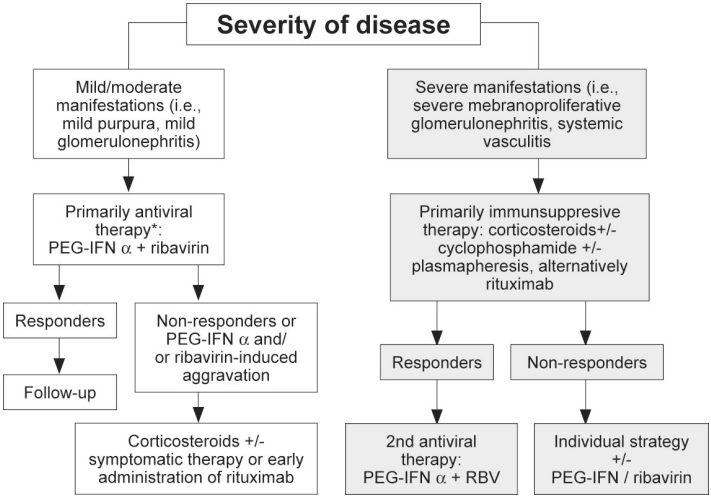

Figure 7.2. Therapy algorithm for symptomatic HCV-related mixed cryoglobulinaemia (modified from Craxi 2008). In patients with severe manifestations, treatment should focus on immunosupression with rituximab (± plasmapheresis).

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 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).

Other Haematological 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. Elthrombopag may be an option. In case of refractory disease or aggravation during the course of antiviral therapy, rituximab should be considered (Weitz 2005).

Autoimmune haemolytic anaemia (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 cryoglobulinaemic or non-cryoglobulinaemic 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 haemolytic anaemia (Fabrizi 2008).

Fulminant manifestations with impending acute renal failure make administration of corticosteroids, immunosuppressive drugs such as cyclophosphamid and eventually plasmapheresis necessary (Garini 2007, Margin 1994). In cases of simultaneous bone marrow B cell infiltration and/or resistance to conventional therapy, application of rituximab is indicated (Roccatello 2004). ACE inhibitors or AT1 receptor antagonists are supplemental (Kamar 2006).

About 13% of HCV-infected patients have **hypothyroidism** and up to 25% have thyroid antibodies (Antonelli 2004). There is evidence that IFN α may induce thyroid disease or unmask preexisting silent thyroidopathies (Graves disease, Hashimoto thyroiditis) (Prummel 2003). Some studies suggest that thyroid autoimmune disorders were significantly present in patients with chronic hepatitis C during but not before IFN α therapy (Vezali 2009). Monitoring of the thyroid function should be performed during treatment.

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

Dermatologic and Other Manifestations

Table 7.3 – Overview

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

8. Management of HCV/HIV Coinfection

Christoph Boesecke, Stefan Mauss and Jürgen Kurt Rockstroh

Epidemiology of HIV and HCV Coinfection

Of the 33.4 million HIV-infected persons worldwide in 2008 it is estimated that at least 5 million of them also have hepatitis C virus infection. Whereas both viruses are transmitted with high efficacy via blood-to-blood contact, HCV is less easily transmitted sexually. Thus, the prevalence of hepatitis C coinfection within different countries, regions and populations is closely related to the prevalence of blood-borne transmission (mainly intravenous drug use) of HIV (Table 8.1).

HCV may well be sexually transmitted and should therefore also be taken into account at regular STD screenings (Gotz 2005, Danta 2007, Vogel 2009a, Vogel 2010). HCV is detected in 4-8% of infants born to HCV-infected mothers (Bevilacqua 2009). However, in HIV/HCV-coinfected mothers receiving HAART and undergoing cesarean section the risk of HCV transmission is reduced to less than 1%. The average estimated risk of transmission for hepatitis C in HIV is depicted in Table 8.2.

Table 8.1 – Geographic differences in coinfection rates.

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

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

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

*With sexual contact the risk refers to cumulative exposure.

Diagnosing HCV in HIV Coinfection

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

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

viremia have been reported in patients who subsequently develop liver failure. Regular monitoring of HCV RNA levels is warranted in HIV/HCV-coinfected patients.

The Natural History of Hepatitis C in HIV-Positive 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). 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-positive T cell responses against HCV (Danta 2008).

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

Effect of Hepatitis C on HIV Infection

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

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

Effect of HAART on Hepatitis C

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

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

Treatment

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

Recently presented data from the PARADIGM trial, a study comparing 800 mg vs 1000/1200 mg of ribavirin plus PEG-IFN in HCV/HIV coinfected patients, showed no significant differences in the success rates (Rodriguez-Torres 2009).

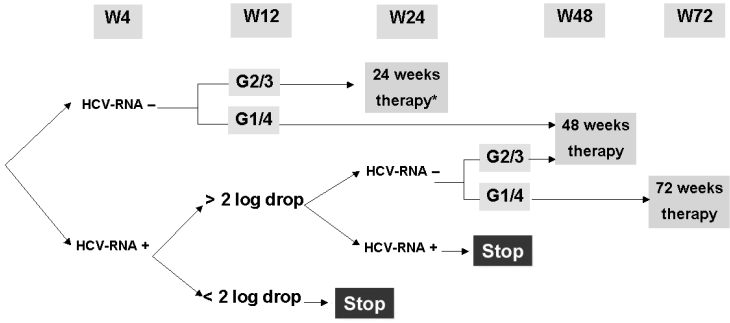

Figure 8.1. Algorithm for management of hepatitis C in HIV coinfection. Proposed optimal duration of HCV therapy in HIV/HCV-coinfected patients (w: week; G: genotype) (modified from Rockstroh 2009a).

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

Noninvasive markers such as blood tests or transient elastography constitute a new means of assessing liver disease in HIV and hepatitis-coinfected individuals (Rockstroh 2009b). When liver biopsy or non-invasive tests for assessing hepatic fibrosis (e.g., elastometry by Fibroscan®, Echosense) demonstrate lower grades of liver fibrosis (F0-F1) regardless of HCV genotype, treatment may be deferred. Assessment of fibrosis should be repeated frequently to monitor progression in these cases.

If chronic hepatitis C is detected early in the course of HIV infection (before the initiation of HAART), treatment for chronic HCV is advised. However, if a coinfected patient has pronounced immune deficiency (CD4 count <200 cells/ml), the CD4 count should be improved via HAART before beginning HCV treatment. Patients with a CD4 relative percentage of >25% are more likely to achieve SVR than those with lower CD4 percentages (Opravil 2008). If an early HCV RNA reduction of at least 2 $\log_{10}$ compared with baseline is not achieved by week 12, treatment should be

discontinued. The current European recommendations for treatment initiation of PEG-INF and ribavirin for HIV/HCV coinfected patients are shown in Figure 8.1.

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

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

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

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

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

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

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

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

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

Antiretrovirals while on HCV therapy

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

Patients on atazanavir may develop jaundice due to an increase in total serum bilirubin levels following initiation of ribavirin (Rodriguez-Novoa 2008). The role of abacavir is

uncertain at this point but cohort data suggest lower success rates (Bani-Sadr 2007).

Table 8.4 summarizes possible interventions for HCV/HIV-coinfected non-responders and relapsers to previous interferon-based therapies (Rockstroh 2008 and 2009a).

Uncontrolled pilot studies of treatment of acute HCV infection in HIV-coinfected patients demonstrate SVR rates above 60% with PEG-IFN monotherapy or combination therapy of PEG-IFN + RBV for 24-48 weeks. HCV RNA levels at weeks 4 and 12 may help guide treatment duration.

Liver Transplantation in HIV/HCV-Coinfected Patients

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

For patients to be eligible for liver transplantation, they need to have either undetectable HIV viremia (<40 copies/ml) or at least treatment options to control HIV infection successfully after liver transplantation. Contraindications for transplantation are opportunistic diseases, ongoing alcohol or drug abuse, HCC metastasis in other organs, a second malignant disease, cardiopulmonary disease, or older age with an elevated risk of mortality related to the operation.

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 cyclosporine A and the ARVs used for HIV therapy. Determinations of the plasma levels of the

antiretroviral drugs are necessary. The doses of cyclosporine A or tacrolimus usually need to be reduced when the patient is treated concomitantly with a protease inhibitor, especially if boosted with ritonavir (Vogel 2004). By contrast, NNRTIs can lower the concentrations of immunosuppressive drugs.

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

Conclusion

Enhanced hepatotoxicity of HAART as well as drug-drug interactions between HAART and ribavirin clearly underline the need for specific treatment strategies.

9. Management of HBV/HCV Coinfection

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Epidemiology

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

Screening

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

Viral Interactions

Coinfected patients may show a large spectrum of virologic profiles (Raimondo 2006). HCV infection can suppress HBV replication and it has been shown that HBV/HCV-coinfected patients have lower HBV DNA levels, decreased activity of HBV DNA polymerase, and decreased expression of HBsAg and hepatitis B core antigen in the liver (Chu 1998). Patients with chronic HBV infection who become superinfected with HCV can undergo seroconversion of HBsAg (Liaw 1994, 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. However, the overall effect appears to be HCV suppression of HBV (Liaw 2001).

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 (Alberti 1995).

HCV superinfection is frequent in HBV endemic areas, such as in Asia (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 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.

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. 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. Treatment studies for HBV/HCV coinfection are reviewed in (Crockett 2005) and (Chu 2008). In patients with HBV/HCV coinfection, treatment should be initiated when inclusion criteria for standard treatment guidelines of HBV or HCV monoinfection are met (see Chapters 4 and 5 for HCV therapy).

In coinfected patients with dominance of HCV infection, IFN plus ribavirin has been well-studied and proven efficient. However, pegylated IFN is the standard of care for HCV monoinfected patients and has been evaluated in recent studies (Potthoff 2008, Senturk 2008, Liu 2009). The combination of PEG-IFN α-2b plus ribavirin was found to induce a sustained HCV RNA response in up to 93% (88% in HCV genotype 1 and 100% in genotype 2 and 3) of coinfected patients (Potthoff 2008).

In patients with dominance of HBV disease, IFN +/- HBV polymerase inhibitor is a possible option. Until now most data available are for lamivudine. There is very little experience with other anti-HBV agents. Future studies are needed to assess the safety and effectiveness of antiviral therapy with pegylated interferon, ribavirin and a combination of the newer nucleoside or nucleotide analogues, such as adefovir, entecavir, telbivudine and tenofovir. Due to loss of viral suppression from the successfully treated dominant virus, deterioration of liver disease has been reported (Yalcin 2003), thus caution must be exercised upon initiation of therapy.

Conclusion

No treatment standard has been established for HBV/HCV-coinfected patients. Treatment decisions must be

made based upon identification of the dominant virus. Recent studies indicate that in patients with dominant HCV replication pegylated IFN plus ribavirin should be the treatment of choice. 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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11. Appendix

Table 11.1 – Pivotal studies investigating early PEG-IFN therapy in patients with acute HCV infection.

Study	n	Treatment	Start of therapy	Duration	Efficacy
Jaeckel 2001	44 in 24 centres	IFN α-2b (4 wks 5 MU daily; 20 wks 5 MU TIW)	89 days after infection (range 30-112 days)	24 weeks	43/44 (98%)
Santantonio 2005	28	PEG-IFN α-2b (1.5 µg/kg/week)	12 wks after onset of disease (17/28 chronic, 16 treated)	24 weeks	15/16 (94%)
Broers 2005	27 (22 IVDU)	PEG-IFN α-2b (1.5 µg/kg/week)	100±82 days after onset of symptoms, 63±82 days after diagnosis (asymptomatic) (22/27 chronic, 14 treated)	24 weeks	8/14 (57%) 7/8 (88%) of adherent pts.
Wiegand 2006	89 in 53 centres	PEG-IFN α-2b (1.5 µg/kg/week)	76 days after infection (range 14-150 days), 27 days after onset of symptoms (range 5-131)	24 weeks	63/89 (71%) 58/65 (89%) of adherent pts.

Table 11.2 – Efficacy of antiviral treatment. SVR depends on HCV genotype, dose and duration of treatment.

Study	Treatment	HCV Genotype	Duration	SVR
Manns 2001	1.5µg/kg PEG-IFN α-2b 800 mg ribavirin	HCV-1	48 weeks	42%
		HCV-2/3	48 weeks	82%
	1.5µg/kg PEG-IFN α-2b >10.6 mg/kg ribavirin	HCV-1	48 weeks	48% (retrospective)
		HCV-2/3	48 weeks	88% (retrospective)
Fried 2002	180µg PEG-IFN α-2a 1000/1200 mg ribavirin	HCV-1	48 weeks	46%
		HCV-2/3	48 weeks	76%
Hadziyannis 2004	180µg PEG-IFN α-2a 800 mg ribavirin	HCV-1	24 weeks	29%
			48 weeks	40%
		HCV-2/3	24 weeks	78%
			48 weeks	73%
	180µg PEG-IFN α-2a 1000/1200 mg ribavirin	HCV-1	24 weeks	41%
			48 weeks	51%
		HCV-2/3	24 weeks	78%
			48 weeks	77%
Zeuzem 2004	1.5µg/kg PEG-IFN α-2b 800-1400 mg ribavirin	HCV-2	24 weeks	93%
		HCV-3		79%
Kamal 2005	1.5µg/kg PEG-IFN α-2b 1000/1200 mg ribavirin	HCV-4	24 weeks	29%
			36 weeks	66%
			48 weeks	69%

Table 11.3 – Optimization of treatment duration in patients with HCV genotypes 2 and 3.

Study	Treatment	Subgroups/Weeks	SVR
Poutschi 2008 N=153	180µg PEG-IFN α-2a 800-1200 mg ribavirin	>600 IU/ml wk 4/24	36%
		<600 IU/ml wk 4/16	82%, 93% if HCV RNA <800,000 IU/ml
		<600 IU/ml wk 4/24	80%, 84% if HCV RNA <800,000 IU/ml
Shiffman 2007a N=1469	180µg PEG-IFN α-2a 800 mg ribavirin	All patients/16	62%
		All patients/24	70%
		<50IU/ml wk 4 (RVR)/16	79%
		<50IU/ml wk 4 (RVR)/24	85%
		<400,000IU/ml wk 0 (LVL)/16	82%
		<400,000IU/ml wk 0 (LVL)/24	81%
Mangia 2005	1.0µg PEG-IFN α-2b 1000-1200 mg ribavirin	Standard group/24	76%
		Standard group/24	91% if wk 4 HCV RNA <50 IU/ml
		>50 IU/ml wk 4 (no RVR)/24	64%
		<50 IU/ml wk 4 (RVR)/12	85%
Dalgard 2008	1.5µg PEG-IFN α-2b 800-1400 mg ribavirin	<50 IU/ml wk 4 (RVR)/14	81% ITT, 86% with F24 HCV RNA test
		<50 IU/ml wk 4 (RVR)/24	91% ITT, 93% with F24 HCV RNA test
		>50 IU/ml wk 4 (no RVR)/24	55% ITT, 59% with F24 HCV RNA test
Manns 2009 N=682	1.0µg PEG-IFN α-2b	All patients/16 (1.5)	57% ITT, 68% as-treated
	1.5µg PEG-IFN α-2b	All patients/24 (1.5)	67% ITT, 82% as-treated
	800-1400 mg ribavirin	All patients/24 (1.0)	64% ITT, 80% as-treated

Table 11.4 – SVR of patients with HCV genotypes 2 or 3 not achieving RVR.

Study	Treatment	Frequency of patients SVR without RVR	SVR without RVR at 24 wks on therapy
Von Wagner 2005	180µg PEG-IFN α-2a 800-1200 mg ribavirin	7% (HCV RNA >600 IU/ml wk 4)	36%
Shiffman 2007a	180µg PEG-IFN α-2a 800 mg ribavirin (24 wk group)	36% (HCV RNA >50 IU/ml wk 4)	45%
Mangia 2005	1.0µg/kg PEG-IFN α-2b 1000-1200 mg ribavirin	36%-38% (HCV RNA >50 IU/ml wk 4)	48-64%
Dalgard 2004	1.5µg/kg PEG-IFN α-2b 800-1400 mg ribavirin	22% (HCV RNA >50 IU/ml wk 4/wk 8)	56%
Dalgard 2008	1.5µg/kg PEG-IFN α-2b 800-1400 mg ribavirin	29% (HCV RNA >50 IU/ml wk 4)	55%

Table 11.5 – Optimization of treatment duration in patients with HCV genotypes 1. Fast responders.

Study	Treatment	**Fast** responders Subgroup	24 Weeks: SVR
Zeuzem 2006	1.5µg/kg PEG-IFN α-2b 800-1400 mg ribavirin	<600,000 IU/ml wk 0 & <29 IU/ml wk 4 (RVR)	89%
Jensen 2006	180 PEG-IFN α-2a 800mg or 1000-1200mg RBV	<600,000 IU/ml wk 0 & <50 IU/ml wk 4 (RVR)	89%
Ferenci 2008	180 PEG-IFN α-2a 1000-1200mg ribavirin (N=120 HCV G1)	<50 IU/ml wk 4 (RVR)	74% ITT, 79% PP

RVR: Rapid virologic response

Table 11.6 – Optimization of treatment duration in patients with HCV genotypes 1. Slow responders.

Study	Treatment	**Slow** responders Subgroup	Weeks: SVR, relapse (R), discontinuation (D)
Sanchez Tapias 2006	180µg PEG-IFN α-2a 800mg ribavirin	>50 IU/ml wk 4 (no RVR)	48: 28%, 53% R, 18% D 72: 44%, 17% R, 36% D
Berg 2006	180µg PEG-IFN α-2a 800mg ribavirin	>50 IU/ml wk 12	48: 17%, 24% D 72: 29%, 41% D
Mangia 2008	180 PEG-IFN α-2a or 1.5µg/kg PEG-IFN α-2b 1000-1200mg ribavirin	>600 IU/ml wk 8 & <600 IU/ml wk 12	48: 38%, 43% R 72: 63%, 15% R
Pearlman 2007	1.5µg/kg PEG-IFN α-2b 800-1400mg ribavirin	≥2 log decline wk 12 & >10 IU/ml wk 12	48: 18%, 59% R, 14% D 72: 38%, 20% R, 15% D
Ferenci 2009	180µg PEG-IFN α-2a 1000-1200mg ribavirin	>50 IU/ml wk 4 (no RVR) ≥2 log decline wk 12	48: 51%, 34% R 72: 59%, 19% R (135µg PEG-IFN after wk 48)
Buti 2009	1.5µg/kg PEG-IFN α-2b 800-1400mg ribavirin	≥2 log decline wk 12 & detectable HCV RNA wk 12	48: 43% ITT, 44% (80/80/80 rule) 72: 48% ITT, 57% (80/80/80 rule)

RVR: Rapid virologic response

Table 11.7 – SVR of IFN/ribavirin or PEG-IFN/ribavirin relapse patients.

Study	Patient population	Treatment	SVR
EPIC3 Poynard 2009	Relapse after 48 weeks PEG-IFN α-2a/ribavirin	1.5 µg/kg PEG-IFN α-2b + 800-1400mg ribavirin	34%
EPIC3 Poynard 2009	Relapse after 48 weeks PEG-IFN α-2b/ribavirin	1.5 µg/kg PEG-IFN α-2b + 800-1400mg ribavirin	32%
EPIC3 Poynard 2009	Relapse after 48 weeks IFN/ribavirin	1.5 µg/kg PEG-IFN α-2b + 800-1400mg ribavirin	43%
Jacobson 2005	Relapse after 48 weeks IFN/ribavirin	1.5 µg/kg PEG-IFN α-2b + 800 mg ribavirin	50%
Jacobson 2005	Relapse after 48 weeks IFN/ribavirin	1.0 µg/kg PEG-IFN α-2b + 1000-1200 mg ribavirin	32%

Table 11.8 – SVR of PEG-IFN/ribavirin in nonresponders.

Study	Patient population	Treatment	SVR
Bocepravir Schiff 2008	Non-responder (null-responder) to PEG-IFN/ribavirin	48 weeks 1.5 µg/kg PEG-IFN α-2b + 800-1400mg ribavirin	2%
EPIC3 Poynard 2009	Non-responder to PEG-IFN α-2a/ribavirin	48 weeks 1.5 µg/kg PEG-IFN α-2b + 800-1400mg ribavirin	6%
EPIC3 Poynard 2009	Non-responder to PEG-IFN α-2b/ribavirin	48 weeks 1.5 µg/kg PEG-IFN α-2b + 800-1400mg ribavirin	7%
REPEAT Marcellin 2008	Non-responder to PEG-IFN α-2b/ribavirin	48 weeks 180µg PEG-IFN α-2a + 1000/1200 mg ribavirin	9%
REPEAT Marcellin 2008	Non-responder to PEG-IFN α-2b/ribavirin	72 weeks 180µg PEG-IFN α-2a + 1000/1200 mg ribavirin	14%
REPEAT Marcellin 2008	Non-responder to PEG-IFN α-2b/ribavirin	48 weeks (Induction) 360/180µg PEG-IFN α-2a + 1000/1200 mg ribavirin	7%
REPEAT Marcellin 2008	Non-responder to PEG-IFN α-2b/ribavirin	72 weeks (Induction) 360/180µg PEG-IFN α-2a + 1000/1200 mg ribavirin	16%
Jacobson 2005	Non-responder to IFN/ribavirin	48 weeks 1.5 µg/kg PEG-IFN α-2b + 800 mg ribavirin	10%
Jacobson 2005	Non-responder to IFN/ribavirin	48 weeks 1.0 µg/kg PEG-IFN α-2b + 1000-1200 mg ribavirin	6%
HALT-C Shiffman 2004	Non-responder to IFN/ribavirin	48 weeks 180µg PEG-IFN α-2a + 1000-1200 mg ribavirin	12%

Index

ABT-333 65
ABT-450 59
ACH-1625 59
adherence 38
ADVANCE trial 53
adverse events 71
albinterferon 69
alisporivir 67
ALT, normal values 42
Amplicor 27
ANA598 65
anti-HCV IgM 26
antidepressants 74
autoimmune haemolytic anaemia 84
BI201335 59
BI207127 65
BILN 2061 58
blood transfusion 14
BMS-650032 59
BMS-790052 66
boceprevir 47, 56
  tolerability 58
branched DNA assay 28
breakthrough 43
cEVR 33
Child-Pugh classification 18
ciluprevir 58
cirrhosis 16, 36
Cobas Amplicor 28
Cobas TaqMan 28
Copegus 34
cryoglobulinaemia 79
cyclophilin B inhibitors 67
danoprevir 59
Debio-025 67
dermatologic manifestations 86
diabetes mellitus 85
diagnosis .....
  acute hepatitis C 30
  chronic hepatitis C 31
diagnostic tests 26
dialysis 43
direct-acting antiviral agents 31, 48
disease progression 17
drug interactions 71
drugs 34
  new drugs 48
early virologic response 33
end of treatment response 33
end-stage liver disease 32
enzyme-linked immunoassays 26
epidemiology 13
eRVR 33
ETR 33
EVR 33
Extended rapid virologic response ... 33
filibuvir 65
genetic marker 39
genotypes 19
genotyping 29
glomerulonephritis 84
GS-9190 65
GS-9256 59
GS-9451 59
HAART 90
HBV/HCV Coinfection 96
HCV 19
  assembly 25
  genome organization 20
  lifecycle 22
  NS5B protein 62
  nucleic acid testing 27
  proteins 21
  quasispecies 60
  RNA replication 24
  structure 19

translation....23
viral entry....23
HCV-796....65
HCV/HIV coinfection....87
liver transplantation....94
hepatic decompensation....16
HIV....14, 67, 87
hypothyroidism....85
IDX184....62, 64
IDX320....59
IL28B....39
ILLUMINATE trial....54
Infergen....34
INFORM trial....66
inosine triphosphatase....39
interferon, pegylated....32, 48
interleukin-29....69
Intron A....34
ITPA....39
kidney transplantation....43
liver fibrosis....36
liver transplantation....42
lymphoproliferative disorders....79
maintenance therapy....45
MALT lymphoma....83
management....
acute hepatitis C....46
chronic hepatitis C....32
diagnostics....31
HCV genotype 1....37
HCV genotype 2 and 3....36
non-responders....45
treatment....32
MELD score....18
mericitabine....62p., 66
MK-5172....59
narlaprevir....59
natural history....
acute hepatitis....15
chronic hepatitis....16
nitazoxanide....68
NM283....62
non-nucleoside analogues....63, 65
non-response....33, 43
NS3....49
NS3-4A protease....49
NS5A inhibitor....65
nucleoside analogues....62
partial response....33
PEG-IFN lambda....69
PEG-IFN α-2a....34
PEG-IFN α-2b....34
Pegasys....34
pEVR....33
PF-00868554....65
PHX1766....59
polymerase inhibitors....62
protease inhibitors....49
PROVE trials....52
PSI-7851....62
PSI-7851....64
qualitative HCV RNA test....27
R1626....62, 64
R7128....62p., 66
R7227....63, 66
rapid virologic response....33
real-time PCR....28
REALIZE trial....54
Rebetol....34
relapse....43
resistance....59
RESPOND trial....57
ribavirin....32, 35, 48
RNA-dependent RNA polymerase....62
Roferon....34
RVR....33
SCH 503034....56
SCH900518....59
serologic assays....26
side effects....39, 71
asthenia....72
autoimmune phenomena....40

boceprevir..... 77
flu-like symptoms..... 40, 71
hypothyroidism..... 72
Interferon alfa (IFN..... 39
psychiatric..... 72
ribavirin..... 42
telaprevir..... 77
weight loss..... 72
signal amplification technique..... 28
silibinin..... 68
SPRINT trial..... 56
sustained virological response 33
SVR..... 33
target amplification technique..... 28
taxonomy..... 19
telaprevir..... 47, 51
different HCV genotypes..... 53
phase III studies..... 53
tolerability..... 54
thrombocytopenia..... 84
TMC435..... 59
transmission..... 14
treatment.....
acute hepatitis C 46
chronic HCV infection..... 35
treatment failure 43
treatment goals..... 33
TruGene..... 30
valopicitabine..... 62, 64
vaniprevir..... 59
VCH-222..... 65
VCH-759..... 65
VCH-916..... 65
Versant HCV RNA Qualitative Assay 28
virological..... 31
VX-950..... 51

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#2

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