the
Flying Publisher Guide to

Hepatitis C Treatment

2011

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2011 Edition

Flying Publisher

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Copy-editing: Simona Ruta and Richard Sebastian Wanless
ISBN: 978-3-942687-04-1

Preface

Affecting around 200 millions people worldwide, chronic Hepatitis C is the leading cause of cirrhosis and liver cancer and the first reason for liver transplants. The current standard therapy for chronic HCV infection – combined pegylated interferon and ribavirin – is successful in only 50% of the cases and is associated with frequent and sometimes serious side effects. Fortunately, there is huge potential to increase the number of successfully treated patients if we take into account pre-treatment and on-treatment host and virus characteristics that may lead to therapy failure.

This Guide will discuss the available strategies for those who interrupt, fail or relapse after treatment, in particular

- the benefits and risks of current therapeutic options
- the categories of patients with therapeutic failure that should be re-treated
- the appropriate measures for therapy monitoring and outcomes assessment

As a growing number of non-responders and relapsers are seen in clinical practice there is a permanent search for new antiviral, anticellular and immunomodulator drugs. Year 2011 has brought the approval of the first generation of viral protease inhibitors that will offer higher cure rates for non-responders and open the door for the eventual testing of interferon-free regimens.

The Editors
June 2011

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Abbreviations

ACR: acute cellular rejection
AEs: Adverse side effects
ALT: alanine aminotransferase
ANC: absolute neutrophil count
AST: aspartate aminotransferase
BMI: body mass index
CP: Child-Pugh
Anti-HCV: antibody to hepatitis C virus
cEVR: complete early virologic response
CIFN: consensus interferon
CHC: chronic hepatitis C
DAA: direct-acting antivirals
DILI: drug-induced liver injuries
EMEA: European Medicines Agency
EoTR: end of treatment virologic response
EVR: early virologic response
FDA: US Food and Drug Administration
HBV: hepatitis B virus
HCV: hepatitis C virus
HCV RNA: ribonucleic acid of hepatitis C virus
HCC: hepatocellular carcinoma
HIV: human immunodeficiency virus
IDUs: injecting drug users
IFN: interferon
IL28B: interleukin 28B
IMPDH: inosine monophosphate dehydrogenase
INR: international normalized ratio
IR: insulin resistance
IU: international unit
LT: liver transplant
MELD: Model for End-Stage Liver Disease
MMF: mycophenolate mofetil
NAT: nucleic acid tests
PCR: polymerase chain reaction
PegIFN: pegylated interferon
pEVR: partial early virologic response
PKR: interferon-inducible proteinkinase
PT: prothrombin time
QoL: quality of life
QALY: quality adjusted life-year
RBV: ribavirin
RGT: response-guided therapy
RVR: rapid virologic response
SNP: single nucleotide polymorphism
SoC: standard of care antiviral therapy
SSRI: selective serotonin reuptake Inhibitor
STAT-C: Specifically targeted antiviral therapy for HCV
SVR: sustained virologic response
TSH: thyroid stimulating hormone
ULN: Upper limit of normal
VL: viral load

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1. Antiviral Therapy: The Basics

Simona Ruta, Costin Cernescu and Richard Sebastian Wanless

The hepatitis C epidemic is still growing in importance. While the incidence of hepatitis C virus (HCV) infections is falling in some countries, the burden of the disease arising from the pool of chronic infections continues to rise. It has been estimated that, by 2030, HCV will cause substantially higher morbidity and mortality than HIV. Chronic Hepatitis C (CHC) occurs in 70% to 80% of those who contract the virus, 20% of whom will progress to cirrhosis within 2-3 decades; a quarter of these will develop decompensated liver disease, hepatocellular carcinoma (HCC) and will need liver transplantation. A recent study has shown that HCV infected persons have three times higher death rates than those of age-matched general population (Brok 2010). Excess mortality is due to both liver related causes and co-morbidities and is related to age, treatment status, the degree of fibrosis and mean alcohol consumption.

Antiviral therapy – Standard of Care (SoC)

According to all consensus guidelines (EASL 2011, NICE 2010, AASLD 2009), the current standard of care (SoC) for CHC is the combination of **pegylated interferon alfa (PegIFN) and ribavirin (RBV) for 24-48 weeks**, depending on the viral genotype.

The primary goal of treatment for CHC is to obtain a s**ustained virological response (SVR), defined as undetectable HCV RNA level at 6 months after treatment completion**. Long-term follow-up studies have shown that 97-100% of sustained responders retain undetectable HCV RNA in serum, and, in many cases, also in liver and peripheral blood mononuclear cells, strongly suggesting that **SVR is associated with eradication of HCV infection.** SVR can be also attained, even if at lower rates, in patients with extensive fibrosis or cirrhosis, decreasing the risk of HCC development and improving the overall survival rates (Dieterich 2009).

The decision to treat or not to treat is made on an individualized basis. Treatment should be considered for all infected patients, particularly for those at risk for progression of liver disease. However, treatment regimens and treatment inclusion criteria have changed over time, as new therapeutic approaches are developed and more individualized regimens are introduced. As we will see in chapter 4, in May 2011, The US Food and Drug Administration (FDA) has approved two new drugs – both viral protease inhibitors – to be used in combination with PegIFN/RBV for the treatment of CHC genotype 1 infection:

- Boceprevir (Victrelis™, Merck)
- Telaprevir (Incivek™, Vertex Pharmaceuticals Inc.)

Interferons (IFNs) are cytokines with species-specific, but non-virus-specific antiviral, immunomodulatory and anticellular activities. PegIFN derives from attachment of an inert polyethyleneglycol (Peg) chain – a unique polymer that does not have a definite tertiary structure – to conventional IFN-alfa. This confers an improved pharmacokinetic profile for the drug, by slowing subcutaneous absorption, reducing degradation and clearance and prolonging its half-life. PegIFN maintains high sustained plasma IFN levels that allow for weekly dosing (compared with 3 times weekly administration of standard IFN), while also reducing its adverse side effects (AEs) and immunogenicity.

There are two FDA and EMA approved formulas of PegIFN that can be administered subcutaneously once weekly, with different dosing regimens and pharmacokinetics (Table 1.1):

- **PegIFN alfa-2a** (PEGASYS™, manufactured by Hofmann La-Roche) in which standard IFN alfa-2a is covalently linked to a 40-kDa branched Peg molecule, administered at a fixed dose (180 μg/week), with a plasma half-life of 80 -160 hours.
- **PegIFN alfa-2b** (PegIntron™, manufactured by Schering–Plough/Merck) in which standard IFN alfa-2b is covalently linked to a 12-kDa linear Peg molecule, dosed according to body weight (1.5 μg/kg/week), with a mean elimination half-life of 40 hours.

Table 1.1 – Different characteristics of the available PegIFNs*

Characteristic	PegIFN alfa-2a	PegIFN alfa-2b
Trade name/ Manufacturer	Pegasys/ Hoffmann-La Roche	PegIntron/ Schering Corporation-now Merck
Structure	large, branched, 40 kD	small, linear, 12 kD
Volume of distribution	8-12 L	0.99 L/kg body
Clearance	60-100 mL/hr	22mL/hr/kg
Absorption half-life (hrs)	50-60	4,6
Elimination half-life (hrs)	65	40
Time to reach maximum concentration	80	15-44
Peak to trough ratio	1.5-2	>10
Cost of combination treatment (PegIFN + RBV) for 24 wks £ †	5019	6743
Cost of treatment 48 wks £ †	10963-11889‡	13468

* According to data from Foster 2010

† according to British national formulary, 50th edition, excluding VAT

‡ depending on body weight

These differences do not affect significantly the treatment outcomes. Current evidence does not allow for a definitive recommendation of one of the two forms of PegIFNs. A Cochrane systematic review of head-to-head randomized trials (Awad

2010) suggests that PegIFN alfa-2a may be associated with an increased benefit in terms of SVR compared to PegIFN alfa-2b, although the largest head-to-head trial (IDEAL study) failed to find a significant difference in SVR rates between the two PegIFN formulations (McHutchison 2009). Nevertheless, the two products seem to be comparable in terms of adverse effects (AEs) leading to treatment discontinuation.

As long as SVR is only a surrogate marker of clinical outcomes (liver failure, HCC and mortality) and the data on the long-term AEs are limited, both regimens seems to be equally effective in the clinical practice.

It is important to mention that **HCV** has notable properties by which it **can inhibit the actions of IFNs**. The HCV protease NS3/4A blocks important proteins and enzymes within the cells (such as IRF3, a key transcriptional regulator of the IFN response, and retinoid-inducible gene 1- RIG1, a growth regulator), leading to a reduction in the expression of IFN-signaling genes (Bode 2008).

Ribavirin (RBV) has both antiviral and immunomodulatory actions. Although RBV monotherapy has little influence against HCV, in combination with interferon it improves dramatically the response rates. Being a guanosine analog, RBV acts by direct inhibition of nucleic acid elongation and of enzymes important in viral replication, such as inosine monophosphate dehydrogenase (IMPDH), as well as by induction of lethal mutagenesis during the viral life-cycle. Although the specific mechanism has not yet been completely elucidated, there is increasing evidence of RBV acting as a true antiviral agent and thus having a critical role in the suppression of viral replication. RBV amplifies the effect of IFN, generating a significant decrease in the relapse rate (Manns 2001, Fried 2002).

Adding RBV to PegIFNs was recommended by consensus in Europe in 1999 and in the United States in 2002. Subsequently, it has been shown that weight–dosed RBV is more effective in acquiring a high rate of therapeutic success. In today's regimens, RBV is administered according to patient's weight: 1000 mg/day

for patients <75 kg and 1200 mg/day for patients >75 kg. Recent clinical trials with new antiviral compounds associated with PegIFN/RBV have demonstrated that maintaining RBV in the therapeutic regimen has an important additive effect.

Predictors of response before treatment

Experienced providers need to take treatment decisions on a case-by-case basis. There are a series of virus, host and treatment characteristics that influence the likelihood of treatment success and are useful when assessing the benefits and risks of therapy.

Virus factors

HCV genotype, pretreatment HCV RNA level (viral load-VL) and the evolution of viral quasispecies (cluster of variant viruses that arise from mutations over time in viral population) are strong independent predictors of SVR to SoC therapy, as well as to triple combination therapy with protease inhibitors.

- **HCV Genotype** is a major predictor of treatment response. HCV genotypes can be ranked, in a decreasing order of susceptibility to IFN-based treatment, as follows: genotypes 2, 3, 4 and 1. Furthermore, subtype 1b rather than 1a and subtype 2b rather than 2a are likely to respond poorer to IFN-based therapy. Permanent viral eradication (SVR) can be achieved in up to 80% of individuals infected with **'favorable' or "easy-to-treat" HCV genotypes (G2/3)**, but only in approximately 40% of those infected with **'unfavorable' or "difficult-to-treat" HCV genotypes (G1/4)**.
- **High baseline VL** (with a cutoff value of 400000 IU/mL) influences negatively the response rate in patients infected with HCV G1 (41% versus 56%), but not significantly in those with HCV G 2/ 3 (74% versus 81%).
- **Higher viral quasispecies complexity** at baseline has been observed in nonresponders compared with sustained

virological responders. Greater sequence heterogeneity generates diverse quasispecies, thereby providing a reservoir of mutations that enable virus-escape from antiviral therapy (Fan 2009).

Host factors

Variation in the IL28B gene region (that encodes IFN-lambda - type III IFN) has been reported by several genome-wide association studies as a **major predictor of HCV treatment response** (Ge 2009, Tanaka 2009, Suppiah 2009) and of viral kinetics during HCV therapy (Rauch 2010).

The presence of the **CC inherited polymorphism** in the IL 28B gene (on chromosome 19 at SNP rs12979860) has been associated with **higher rates of therapeutic success**, especially for genotypes 1 and 4, compared with the presence of CT or TT polymorhisms. The same is true for HCV co-infection with HIV (Medrano 2010). **Alleles frequencies differ between racial groups**, the favorable CC polymorphism being most frequently encountered in Asians and least frequently in African-Americans, explaining, at least partially, the differences in the treatment response between races (Ge 2009, Thomas 2009). The same polymorphism in the IL28B gene is a **determinant of natural HCV clearance** (Thomas 2009) and is **associated with lower pretreatment levels of ISG** (Thompson 2010). In transplanted individuals, both donor and recipient IL28B genotypes influence the response to HCV therapy (Fukuhara 2010).

Host immune response. The baseline pretreatment level of IP-10 (CXCL10 – a chemochine active on lymphocytes) in plasma and the intrahepatic IP-10 mRNA are elevated in patients chronically infected with HCV genotypes 1/4 who do not achieve SVR (Lagging 2011).

Other host-related negative predictors of response include older age, male sex, black race, high body mass index (BMI) and presence of co-morbitities.

Age. Younger patients (<40 years) have higher SVR rates with SoC. Nonresponders tend to be on average 5 years older than sustained responders (Hadziyannis 2004). Therapy is generally deferred in elderly patients with comorbid conditions since these may be exacerbated by combination therapy with PegIFN/RBV. Despite all these observations, age alone should not preclude antiviral therapy, and treatment decisions should be made on a case by case basis.

The efficacy and safety of the PegIFN/RBVcombination is also evaluated for pediatric patients. Only a limited number of children with HCV infection cleared viremia spontaneously over a decade of follow-up, and those who did were more likely to be infected with G3. Persistent viral replication led to end-stage liver disease in a small subgroup characterized by perinatal exposure, maternal drug use, and infection with HCV G1a. Children with such features should be considered for early treatment. After treating children, SVR was attained in 65% of the cases, genotype being the main predictor of response (G1: 53%; G2/3: 93%; G4: 80%). The rate of SVR was similar in younger and older children. Baseline VL was the main predictor of response in the G1 cohort. AEs were generally mild or moderate in severity (Wirth 2010).

Race. Racial differences in the response to PegIFN/RBV therapy have been signaled, with Hispanics and African-Americans less likely to respond compared to Whites or Taiwanese patients (Ghany 2009).

Co-morbidities

Obesity and its histological correlate, **steatosis**, are common determinants of liver disease progression in HCV infection. We must keep in mind that "not all hepatic fat is alike" and that the etiology of steatosis makes an important difference in the progression of hepatic fibrosis, the development of HCC, extrahepatic manifestations, and prognosis.

Patients with BMI>30 kg/m2 are more likely to be insulin-resistant, to have more advanced hepatic steatosis or fibrosis

and to experience a reduced response to combination therapy (Khattab 2010).

Insulin resistance (IR) is one of the strongest negative predictors of response to HCV therapy. Improved insulin sensitivity may be associated with better treatment response and even with HCV clearance. It is important to control diabetes before starting PegIFN/RBV therapy, because IFN induces a decrease in glucose uptake by peripheral tissue and the liver. New HCV protease inhibitors can restore insulin sensitivity in patients chronically infected with G1 HCV. HCV G3 has a direct steatogenic effect independent of IR.

Co-infections. Patients with human immunodeficiency virus-**HIV-HCV coinfection** have been shown to respond less favorably to antiviral therapy than patients infected with HCV alone. Moreover, serious AEs were far more frequent (35%) than have been reported among HIV-seronegative patients (10-15%). However, co-infected patients have a rapid fibrosis progression rate and experience complications of portal hypertension and PegIFN/RBV should be initiated, if treatment response outweigh the risks of complications from the AEs of therapy (see chapter 3 for details).

Dual infections of HCV and hepatitis B virus (HBV) occur in up to 5% of the general population in HCV-endemic areas and lead to more severe liver disease. Recently, a large, open-label, comparative multicenter study confirmed the efficacy of PegIFN/RBV for patients with chronic HCV-HBV dual infection in Taiwan (Jamma 2010).

Treatment related factors

The key components of therapy that affect the success rate are: the optimal duration of therapy (48 or 24 weeks depending on the viral genotype), the need for different regimens for patients with G1/4 versus G2/3 infections, the appropriate doses of both PegIFN and RBV and the effective management of the treatment-associated side effects (Ferenci 2008).

Treatment interruption due to AEs are more frequent in patients receiving PegIFN/RBV for the longer duration of 48 weeks.

All studies show the importance of **adherence** (McHutchison 2002) using the 80/80/80 rule (patients who took more than 80% of their prescribed IFN, more than 80% of their prescribed RBV, and are treated for more than 80% of the planned treatment duration). Adherence seems to be influenced by several patients' baseline characteristics: HIV coinfection; previous HCV treatment regimen; use of illicit drugs.

Adverse effects associated with therapy

In clinical trials, approximately 10–15% of patients discontinue PegIFN/RBV therapy due to AEs; however, in clinical practice, the rate of treatment withdrawal has been reported to be substantially higher.

In addition, dose reduction of PegIFN and/or RBV owing to AEs is necessary in 25–40% of patients (especially in elderly and in those with low baseline hemoglobin level). Importantly, dose reduction should be implemented at the earliest possible stage, when slight signs of AEs are noted. Combination therapy should then be prolonged to ensure the full scheduled doses of therapy.

Regional and global variability exists in the nature of AEs and in the strategies employed to mitigate their impact (Sulkowsky 2011).

Influenza-like symptoms (such as fatigue, headache, fever, and rigors) occur in virtually all patients after the first doses of PegIFN, but usually subside after the first month of treatment. Dermatologic effects (alopecia, dermatitis) and gastrointestinal symptoms (nausea, diarrhea) are also very frequent. The most prevailing severe AEs are

- hematologic
- neuropsychiatric
- autoimmune

Anemia occurrs in more than 30% of treated patients. Usually, the lowest hemoglobin (Hb) values are recorded 6-8 weeks after

treatment initiation and stay at the same level throughout the remaining therapy period, up to 48 weeks. Severe anemia, with hemoglobin levels <10 g/dL, occur in approximately 10 - 15% of patients. IFN induces bone marrow suppression, while RBV cause hemolytic anemia. Recently, genome-wide association studies have identified an inherited genetic polymorphism at chromosome 20, in the inosine triphosphatase gene (SNPs: rs1127354 and rs7270101), as predictive for RBV induced anemia (Fellay 2010). The presence of A/A and A/C vs. C/C genotypes predicts protection from RBV induced hemolytic anemia during the early stages of treatment.

The management of anemia follows several successive steps:

- RBV dose reduction by 200-400 mg/day, when Hb level decreases between 8.5 - 10 g /dl;
- Discontinuation of RBV when Hb level declines to <8.5g/dl;
- Epoetin administration in patients with early onset of anemia, in order to prevent treatment interruption. Use of recombinant human erythropoietin-stimulating agents has been associated with higher SVR rates and with reduced dropout rates (Sulkowski 2009).

RBV induced anemia can precipitate occult coronary artery disease, especially in older patients (due to age related reduction in creatinine clearance). An accurate estimation of the glomerular filtration rate and the administration of a lower dose of RBV are recommendable in elderly patients.

Neutropenia (with absolute neutrophil count – ANC less than 1.5 x10^9/mL) and **thrombocytopenia** (less than 50 000 cells/mm3) are also common. Consequently, eligibility for treatment may be restricted in patients with advanced liver cirrhosis.

The following decision tree is recommended for the management of neutropenia and thrombocytopenia:

- PegIFN dose reduction, when ANC< 750 cells/mm3 and platelets count < 50,000 cells/mm3;
- treatment discontinuation, when ANC < 500 cells/mm3 and platelets count< 25,000 cells/mm3. If neutrophils or platelets

counts go up, treatment can be restarted, but at a reduced Peg IFN dose;
- use of stimulating factors (i.e. Filgastrim™ - granulocyte macrophage colony stimulating factor or Eltrombopag™ -an oral thrombopoietin receptor agonist) is not routinely recommended in clinical practice, except for patients with cirrhosis.

Neuropsychiatric symptoms such as depression, irritability, insomnia, and, occasionally, aggressive behavior are some of the most debilitating AEs of PegIFN therapy, occurring in approximately 20% to 30% of patients after the first month of treatment. Interventions may require an initial dose reduction, followed by permanent discontinuation of IFN in the case of persistently severe or worsening symptoms. In most cases, the neuropsychiatric symptoms resolve after PegIFN discontinuation. A multidisciplinary approach, including medical treatment (administration of antidepressants – especially serotonin uptake inhibitors and benzodiazepines, when required) and psychiatric counseling is needed in order to reduce the psychiatric side effects of antiviral therapy.

Autoimmune disorders involve most commonly the development of autoimmune thyroiditis, but HCV infection has been also related to mixed cryoglobulinemia, thyroid dysfunction and papillary thyroid cancer. There is ample evidence showing that 7–11% of HCV-infected patients have thyroid dysfunction (frequently consistent with hypothyroidism, with increases in thyroid-stimulating hormone -TSH and decreases in free thyroxin -T4 -mean values) prior to the initiation of treatment. This percentage goes up to 15-20%, once combined PegIFN/RBV therapy is initiated. Thyroid function should be monitored routinely before and during treatment, with TSH and T4 levels measured every 12 weeks while on therapy and again at 6 months after the end of treatment. Specific therapy may be needed to maintain a euthyroid state.

A series of other side effects are reported at lower rates, such as pulmonary (cough, dyspnea), cardiovascular (cardiomyopaty,

hypertension, supraventricular arrhythmias and myocardial infarction) and ocular (retinal abnormalities).

Usually, but not always, these side effects reverse within a short period after the end of therapy. Extreme caution is however recommended in patients with preexisting chronic obstructive pulmonary disease, diabetes mellitus prone to ketoacidosis, severe myelosuppression, and/or coagulation disorders (including thrombophlebitis and pulmonary embolism). RBV may cause birth defects and/or death of the unborn infant. Pregnancy must be avoided in female patients and in female partners of male patients.

Recognition and effective management of AEs are critical components of the successful treatment of CHC. Additional measures include life style modification (hypocaloric diet, physical exercise) in order to decrease the BMI and to prevent weight gain. There are reports suggesting the beneficial effects of insulin sensitizers (Metformin™- to reduce hepatic gluconeogenesis and Pioglitazone™ -to sensitize insulin receptors and mobilize visceral fat to subcutaneous tissues). A series of hepatoprotective drugs and antioxidants (vitamin E, betaine, silymarin and β-carotine) inhibit the toxic effects of free radicals and prevent the synthesis of proinflammatory cytokines that promote steatosis (El-Zayadi 2009). Excessive alcohol use could reduce the likelihood of therapy response and abstinence should be recommended before and during treatment.

Response-guided therapy (RGT)

RGT is a dynamic algorithm that involves individualized treatment based on the on-treatment virologic response. Basically, the more rapidly HCV RNA becomes negative during treatment, the higher the rate of SVR.

Several types of virological responses may occur, categorized according to their timing during treatment (Di Bisceglie 2007, McHutchinson 2009):

- **rapid virological response (RVR)**: undetectable HCV RNA at week 4 (measured by real-time PCR assay with lower limit of detection <15 IU/mL)
- **early virological response (EVR)**, assessed at week 12
- **complete EVR (cEVR)**: undetectable HCV RNA at week 12
- **partial EVR (pEVR)**: decrease of HCV RNA by >2 $\log_{10}$ (100 fold) from baseline values at week 12
- **end-of-treatment virological response** (EoTR): undetectable HCV RNA at the end of therapy (week 24 for genotypes 2/3 or week 48 for genotypes 1/4)
- **sustained virologic response (SVR)**: undetectable HCV RNA 6 months after completing therapy

The standard recommended duration of treatment (Table 1.2) is **48 weeks for HCV genotypes 1/4** (with SVR rates of about 50% and 65%, respectively) and **24 week for genotypes 2/3** (with SVR rates of more than 75%). There is so far insufficient experience to provide recommendations for HCV genotypes 5/6. High weight-based dose RBV (15 mg/kg body) is recommended for patients with baseline factors suggesting low responsiveness (IR, metabolic syndrome, severe fibrosis or cirrhosis, older age).

The most important marker of treatment success is SVR. An EoTR does not accurately predict a SVR, but is necessary for it to occur. A RVR is the best predictor of SVR, if patients fulfill the complete duration of treatment. The absence of an EVR is highly predictive of treatment failure.

Treatment should be stopped at

- week 12 if the HCV RNA decrease is less than 2 $\log_{10}$ IU/ml, compared with the baseline value (the SVR rate in these patients is less than 2%)
- week 24 in patients with detectable HCV RNA (>50 IU/ml), due to a minimal chance of SVR (1–3%)

Table 1.2 – First-line treatment recommendations for antiviral therapy in Hepatitis C*

HCV Genotypes	PegIFN alfa-2a once per week	PegIFN alfa-2b once per week	RBV once per **day**	Planned duration†
1 and 4	180 µg Flat dose	1.5 µg/kg weight-based dose	15 mg/kg weight-based dose	48 weeks
2 and 3	180 µg Flat dose	1.5 µg/kg weight-based dose	800 mg daily flat dose, if BMI<25 15 mg/kg weight-based dose, if BMI>25	24 weeks

*According to data from EASLD 2011

†Treatment duration should be tailored to the on-treatment virological response at weeks 4 and 12, and eventually, week 24.

For RGT, the following **recommendations** can be made (Tsubota 2011):

- Treatment duration can be reduced to 12 weeks for genotypes 2/3 infected patients who obtain an RVR with PegIFN and weight-based RBV dosing. This does not compromise the likelihood of achieving an SVR, but reduce the AEs and the associated costs.
- Treatment duration can be reduced to 24 weeks for genotype 1 infected patients with low baseline (pretreatment) VL who attain a RVR.
- Treatment may be extended to 72 weeks for genotype 1 infected patients who show a slow virological response (with partial EVR and HCV RNA negative by week 24). However, for those who do not attain an EVR, the chance of treatment success is very low (Thomson 2008).

In the clinical trials of the new direct-acting antivirals, a new marker has been implemented, namely extended RVR (Sherman 2010). **Extended RVR (eRVR)** is defined as undetectable HCV RNA at week 4 of therapy, maintained through a later time point (in some cases over a period of 12 weeks, in others over 24 weeks). eRVR is a good predictor of the ability to shorten triple therapy with protease inhibitors. Patients with G1 HCV, who

obtain an eRVR under triple therapy containing a protease inhibitor, are eligible for RGT and a shortened duration of treatment (24 weeks). Failure to achieve an eRVR cannot be used as a stopping rule; continuation of therapy leads to SVR in a considerable number of patients.

Nonresponders and relapsers

Using on-treatment viral kinetics, the following categories of **treatment failure** can be defined:

- **virologic breakthrough**: HCV RNA reappearance while still on treatment
- **virologic relapse:** undetectable HCV RNA at the end of therapy, but HCV RNA reappearance after completion of therapy
- **nonresponse:** failure to achieve undetectable HCV RNA throughout treatment

Further detailing of the nonresponse category have been made based on the observation that SVR rates are significantly higher if more than 1 $\log_{10}$ reduction was registered at week 12 (Zeuzem 2011):

- **null responders** – patients with <2 $\log_{10}$ decrease in HCV RNA level by week 12, who never reach undetectable levels throughout the course of treatment
- **partial responders** – patients with >2 $\log_{10}$ decrease by week 12, despite remaining detectable during treatment

All HCV-infected individuals who fail to respond or who relapse have a series of pre-treatment and on-treatment **fixed** factors (genotypes 1/4, advanced fibrosis, older age, race and genetic background- risk alleles at IL28B gene (CT or particularly TT) or/and **correctable** factors (patient adherence, AEs associated with therapy) that contribute to the therapy failure (Missiha 2008). Overcoming these obstacles substantially increase the chances for success, as will be shown in detail in chapter 3. Moreover, failure to eradicate HCV infection does not mean that the patient is non-responsive to therapy, as most patients

improve biochemically and histologically. Therapeutic options for these individuals include (AISF 2009):

- Retreatment with current SoC; the use of higher doses and/or extended duration of treatment, maintenance therapy with PegIFN – described in detail in chapter 3.
- The use of newly developed direct-acting antivirals (DAA) – described in detail in chapter 4.

The overall objectives of new therapeutic strategies are to prevent complications of end-stage liver disease and death from HCV infection. In this respect, patients with compensated cirrhosis are candidate for (re)treatment in order to prevent decompensation. For patients with decompensated disease the aim of treatment is to improve survival, while waiting for liver transplant. The benefits and challenges posed by these approaches are detailed in chapter 5.

Outlook

The management of patients with CHC is complex and challenging, due to the potential AEs of antiviral therapies and common co-morbidities often found in this group of patients. Studies have shown that a multidisciplinary team-based management approach can improve treatment outcomes in a cost-effective manner.

Early treatment involves providing SoC therapy to all patients with mild disease, some of whom will never progress to the moderate to severe stage. This approach is associated with increased costs per quality-adjusted lifeyears (QALY) gains. Moreover, drug costs and excess costs for monitoring patients are all incurred in the first year of the strategy, rather than at a future date determined by the rate of disease progression (Hartwell 2011).

In contrast, **the watchful waiting strategy** involves providing antiviral treatment only to those patients with disease progression. This is mostly based on the fact that although antiviral therapy prevents complications and decreases the overall severity and duration of the illness, its long-term benefit

on the morbidity and mortality associated with chronic infection is poorly quantified.

The best choice for treatment initiation is made on a case by case basis. Individulised decisions are based on a thorough pre-treatment assessment of the virus, host and other associated factors that contribute to treatment failure. **Response-guided therapy** has demonstrated significant advantages compared to the watchful waiting strategy.

The decision regarding retreatment of patients with advanced liver diseases depends on clinical factors like expected progression of diseases, degree of inflammation/fibrosis, coinfection with HIV or/and HBV, co-morbidities (autoimmune diseases, heart and renal failure). Furthermore, modified regimens, with currently available medications, novel modified IFNs and RBV or combinations with direct-acting antivirals (DAAs), are developed. A more active and highly individualized therapeutic strategy is a priority for nonresponders to current SoC.

Links

- **European Association for the Study of the Liver** (EASLD) http://www.easl.eu/clinical-practice-guideline
- **The American Association for the Study of Liver Diseases** (AASLD) http://www.aasld.org/practiceguidelines
- **National Institute for Health and Clinical Excellence** http://www.nice.org.uk

2. Patients' monitoring during and after treatment

Simona Ruta and Costin Cernescu

Basic knowledge

Hepatitis C may be clinically silent for years and many people have been infected with hepatitis C virus (HCV) for decades without knowing it. Effective screening should focus on populations at-risk for HCV infection. Hepatitis C is diagnosed by simple blood tests (Dufour 2000) (Table 2.1):

Detection of HCV antibodies is done by enzyme immunoassay (screening tests) and immunoblot (confirmation tests). A new HCV rapid test device (OraQuick® HCV Rapid Antibody Test), was approved recently in Europe for use with venous or fingerstick blood, serum, plasma or oral fluid (Lee 2011). This may help address the problem of under-diagnosis, by increasing testing outside of traditional clinical settings. However, all these techniques have a window-period limitation (due to the late seroconversion), which can last 70-82 days, considerably reducing their usefulness in the diagnosis of acute HCV infection. Testing for anti-HCV may be performed at 18 months of age or older (before this age there is a high rate of false

positive results, due to passive antibodies transfer from the mother).

Nucleic acid testing (NAT) – detection of presence and/or amount (viral load – VL) of HCV RNA in the blood, reflects the actual viral replication. These tests are the hallmark of HCV diagnosis in both antibody-positive and negative patients, with unexplained ALT elevations or liver disease documented by liver biopsy (LB). A high VL is a negative predictor of therapeutic success. Sequential VL measurements with the same method during treatment (at weeks 4, 12, 24/48) and 6 month after treatment completion inform response-guided therapy (RGT).

Table 2.1 – Blood tests for hepatitis C

Test/Type	Application	Comments
EIA (enzyme immunoassay)	Indicates past or present infection	Does not differentiate between acute and chronic infection
All positive EIA results should be checked with a supplemental HCV RNA assay:		
HCV RNA qualitative (RT-PCR)	Detects virus as early as 1-2 weeks after infection. Useful for reduction of residual risk associated to transfusions*	Presence of circulating HCV RNA might be intermittent
A single negative RT-PCR is not conclusive		
HCV RNA quantitative (Real-time PCR)	Determines concentration of HCV RNA (VL)	Useful for assessing the response to therapy
HCV RNA genotyping	Groups isolates of HCV based on major genetic types and subtypes	Determines the length of treatment and prediction of SVR rate

* screening by Versant™ (Siemens Health Care Diagnostics) and Procleix™ HIV-1/HCV assays (Gen-Probe).

Determination of HCV genotype. The molecular characterization of genotypes and subtypes of HCV is particularly important for the response to treatment and disease prognosis (Scott 2007). There are 6 major genotypes of HCV and more than 50 subtypes.

Viral kinetics: methodology

Measuring VL at baseline, as well as early after treatment initiation may help to predict response and determine the optimal length of therapy. As shown in chapter 1, in order to maximize treatment effectiveness, while minimizing toxicity, the optimal duration of PegIFN/RBV therapy is determined by viral genotype, with additional guidance provided by the on-treatment response (RVR being an earlier predictor of treatment success and EVR an accurate predictor of treatment failure).

Viral load monitoring

For HCV RNA measurement, different standardized quantification assays, based on **signal amplification** [branched DNA(bDNA) assay] and **target amplification** [reverse-transcription PCR (RT-PCR)] with different sensitivities are commercially available. The development of a World Health Organization HCV international unit (IU) standard has contributed to a better accuracy and comparability of results obtained by different assays. However, since standardization to IU and the calibration of assay sensitivity are based on genotype 1a (deLeuw 2011), relative quantification results may vary among assays. Using the WHO international standard, a VL of 2 millions copies/mL (the cut-off value predictive for therapeutic success in early clinical trials with IFN) was found to correspond to 800 000 IU/mL. Currently a cut-off of 400 000-800 000 IU/ml separate low from high VL. Further studies have found that patients with low baseline HCV RNA levels have a 15-39% better response rate, a finding that is consistent across trials using different formulations and dosages of IFN (Strader 2004).

Real-time PCR tests

Real-time PCR tests are faster and more cost-effective methods that detect very low VL (10-15 IU/ml) (Vermehren 2008). Real-time PCR can accurately quantify HCV RNA levels over a linear range exceeding 6 logs (10 IU/mL to 100 million IU/mL) (Table

2.2). Therefore, a single test result serves the purpose of both quantitative and qualitative HCV NAT with similar sensitivity (Ogawa 2010).

Table 2.2 – Currently available HCV RNA quantification methods*

Assay	Manufacturer	Method	Conversion Factor (copies/mL)	Dynamic Range (IU/mL)
Cobas Taqman HCV Test	Roche Molecular Systems	Real time PCR	3.4	43-69,000,000
Abbott Real-Time PCR	Abbott Diagnostics	Real time PCR	3.4	12-100,000,000
LCx HCV RNA Quantitative	Abbott Diagnostics	RT-PCR	3.8	25-2,630,000
SuperQuant	National Genetics Institute	RT-PCR	3.4	30-1,470,000
Versant HCV RNA 3.0 Assay	Siemens Health Care Diagnostics	bDNA	5.2	615-7,700,000

* According to data from Vermehren 2008 and Ghany 2009

Minimal residual viremia might be predictive of post-treatment relapse (Matsuura 2009). Rules for treatment duration and early discontinuation were mainly established with NAT assays with a detection limit of 50 IU/ml. Lower detection limits (undetectable VL defined as less than 15 IU/ml) did not significantly influence the SVR rates after shortened treatment duration, for patients with RVR (82% for G1 infected patients treated for 24 weeks and 95% for G2/3 infected patients treated for 16 weeks) (Sarrazin 2010).

The assay's choice should be tailored to the dominant genotype in the study population, as some assays have been reported to substantially underestimate HCV RNA levels in certain genotypes. The same assay should be used for all samples from a single patient and, whenever possible, throughout the clinical development program.

HCV genotyping

HCV genotyping should be performed in all HCV-infected persons prior to treatment initiation in order to plan for the duration of therapy and to estimate the likelihood of response. An assay based on viral population sequencing, reverse hybridization or real-time PCR, which has been validated for correct subtyping of at least subtypes 1a and 1b should be used. Two commercial assays are frequently used for HCV genotypes:

- TruGene™ HCV Genotyping kit (Siemens Healthcare Diagnostics Division, Tarrytown, NY), based on direct sequence analysis of the 5' UTR (untranslated region),
- Versant™ HCV Genotype Assay LiPA (version I; Siemens Medical Solutions, Diagnostics Division, Fernwald, Germany), based on reverse hybridization analysis with genotype-specific oligonucleotide probes binding to the 5' UTR. A second generation line probe assay (LiPA) contains probes targeting both the 5' UTR and the core regions of the viral genome, improving the accuracy of discrimination between subtypes 1a and 1b.

A new test which uses real-time PCR technology for HCV genotyping has recently been developed by Abbott Molecular.

HCV resistance monitoring. Like HIV and HBV, HCV has a high replication rate and replicates via an error-prone mechanism, generating resistance variants. In the near future, HCV resistance testing (Kieffer 2010) will most probably be part of the clinical monitoring algorithms. Assays based on viral population sequencing require a minimum VL of 1000 IU/mL and define the most common mutation patterns, without detecting the low-frequency variants. Accurate determination of viral genotype/subtype is critical for resistance testing during the development of new direct-acting antivirals (DAAs) (Chevaliez 2009).

Pretreatment samples are analyzed to detect known or novel predominant viral polymorphisms and to provide the

comparator for mutations emerging at later time points, during or after treatment. On-treatment viremic samples are analyzed to determine specific changes associated with decreased susceptibility and virologic failure. Post-treatment samples are analyzed for persistence or loss of resistant variants and may help distinguish between re-infection and relapse. More details on the impact of resistance on HCV treatment are given in chapter 4.

Assessment of hepatic fibrosis

CHC may progress to cirrhosis (in approximately 20% of patients, with a mean duration of 20 years) and subsequently, decompensation and complications, including HCC, develop in about 30% of cases over a period of approximately 4 years (DiBisceglie 2008). Histologically significant liver disease can be also present in patients without symptoms and with normal ALT levels. In theses cases, deferring treatment until liver function is depressed (low albumin, altered PT) may decrease SVR rate and increase the risk of AEs (Pradat 2002). Evaluation of liver fibrosis is thus compulsory (Table 2.3).

Liver biopsy

Liver biopsy (LB) is the gold standard for (*i*) liver disease staging, (*ii*) treatment decisions and (*iii*) prognostication, as it may reveal advanced fibrosis or cirrhosis that necessitates surveillance for HCC and/or screening for varices.

Before treatment LB is indicated for prognostic purposes and guiding treatment decisions. If LB shows significant fibrosis treatment should be initiated, otherwise, treatment can be deferred (Afdhal 2009). Individualized treatment decisions are based on the severity of liver disease. Treatment is indicated in patients with compensated cirrhosis provided they do not have contraindications to therapy.

Post-treatment LB is essential to demonstrate regression of cirrhosis after viral supression. It is not recommended for assessment of the efficacy of therapeutic regimens, unless hepatic safety issues impose it.

Table 2.3 – Liver fibrosis evaluation methods*

Methods	Categories	Classification	Comments
1) Invasive	Liver biopsy	Percutaneous Laparoscopic	Scoring systems are presented in Table 2.4
2) Non-invasive	Serum biochemistry	Indirect markers	Biomarker combinations or composite indexes
		Direct markers	Reflect extra cellular matrix removal/deposition, the balance between hepatic fibrogenesis and fibrolysis, or cytokines (TGF-β 1† and PDGF†) associated with fibrosis
	Imaging techniques	Elastography Ultrasonography CT, MRI, PET	Fibroscan® is the most used technique
	Genetic markers		Estimate the transdifferentiation of hepatic stellate cells to myofibroblasts

* According to data from Ahmad 2011.

† TGF-β1: transforming growth factors β1; PDGF: platelet derived growth factor

Different **scoring systems** (Table 2.4) have been defined in order to classify the extent of necroinflammatory activity **(grading)** and the extent of fibrosis **(staging)** in LB.

However, LB is invasive and has a number of drawbacks:

- substantial sampling error (extracts only 1/50,000 of the liver)
- variability in interpretation
- potential serious adverse outcomes (bleeding)
- high cost (approximately $1000–$1500 per biopsy)
- low patient's acceptability/reluctance to undergo repeated biopsies

Table 2.4 – Scoring systems for histological stage*

Stage	IASL (Desmet 1994)	Batts-Ludwig (Batts 1995)	Metavir (Bedossa 1996)	Ishak (Ishak 1995)
0	No fibrosis	No fibrosis	No fibrosis	No fibrosis
1	Mild fibrosis	Fibrous portal expansion	Periportal fibrotic expansion	Fibrous expansion of **some** portal areas with or without short fibrous septa
2	Moderate fibrosis	Rare bridges or septae	Periportal septae	Fibrous expansion of **most** portal areas with or without short fibrous septa
3	Severe fibrosis	Numerous bridges or septae	Porto-central septae	Fibrous expansion of most portal areas with **occasional** portal to portal **bridging**
4	Cirrhosis	Cirrhosis	Cirrhosis	Fibrous expansion of most portal areas with **marked bridging**
5				Marked bridging with **occasional nodules**
6				Cirrhosis

* According to data from Ghany 2009.

Non invasive methods

Non-invasive assessment of liver fibrosis based on either biochemical methods or imaging techniques have emerged over the past ten years as an alternative to the systematic use of LB. These methods are easy-to-do, reliable and can be repeated in follow-up visits. However, these noninvasive tests are more adequate for identifying patients with advanced fibrosis/cirrhosis than in differentiating those with moderate and mild fibrosis. According to the current recommendations, these methods should not replace LB in routine clinical practice. **Transient elastography (FibroScan™)** uses ultrasound and low frequency elastic waves to measure liver elasticity/stiffness in kilopascals (kPa).

With a cutoff value of about 7-8 kPa, it can identify about 70% of patients with histological signs of moderate to severe fibrosis. With a cutoff of 14-15 kPa, it can identify about 85% of patients with histological signs of cirrhosis.
Transient elastography is less reliable in ruling out moderate fibrosis. The results are less certain in patients with a thick chest wall, hepatic congestion of cardiac origin and acute exacerbations of hepatitis. However, it has improved the ability to define the extent of fibrosis without a LB, particularly when combined with other noninvasive markers.
Biochemical scores are calculated based on panels of multiple serum markers associated with hepatic fibrosis. Performance of these measures appears similar in both HCV monoinfected and HIV-HCV co-infected patients (Shaheen 2008). Several simple tests are presented in Table 2.5.

Two tests have been specifically designed for **HIV-HCV co-infection: SHASTA index** (includes hyaluronic acid, AST and albumin) (Kelleher 2005) and **FIB-4** (ALT and AST level, platelet count and age) (Sterling 2006).

Table 2.5 – Simple biochemical scores

Test	Markers	Interpretation
AAR (Williams 1998)	AST to ALT *ratio	AST/ALT ≥ 1: significant cirrhosis
APRI (Wai 2003)	AST-platelet ratio	APRI < 0.5: no/minimal fibrosis APRI > 1.5: significant fibrosis
Fibrosis Index (FI) (Ohta 2006)	Platlet count and serum albumin	FI < 2.1: no/ minimal fibrosis FI ≥ 2.1: significant fibrosis FI ≥ 3.3: cirrhosis

* AST: aspartate aminotransferase; ALT: alanine aminotransferase

Several **composite tests** based on mathematical algorithms have been introduced in practice (Table 2.6).

Table 2.6 – Composite biochemical scores

Test	Markers	Interpretation
FibroTest™ (Imbert-Bismut 2001)	alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, GGT, bilirubin	Result is provided as a score of 0 to 1, proportional to the severity of the fibrosis, with conversion to the METAVIR system (from F0 to F4).
HepaScore™ (Adams 2005)	alpha 2 -macroglobulin GGT*, bilirubin, hyaluronic acid, age, gender	A HepaScore <0.55 is considered "negative" and indicates a METAVIR score of F0 or F1. A HepaScore ≥0.55 is considered "positive" and indicates a METAVIR score of F2 to F4.
FibroMeter™ (Cales 2005)	alpha2–macroglobulin, hyaluronic acid, platelets, prothrombin index, AST, urea, age, gender	FibroMeter™ has two main diagnostic targets (fibrosis stage and area of fibrosis), being adapted for special explicit causes†.

* GGT: γ-glutamyltranspeptidase

† chronic viral hepatitis B or C, alcoholic liver disease and non-alcoholic fatty liver disease

FibroTest™ (Biopredictive, Paris, France) identifies about 70% of patients with histological signs of moderate to severe fibrosis and about 90% of patients with histological signs of cirrhosis, using the manufacturers' recommended cutoff values. The FibroTest™ together with FibroScan™ have excellent utility for the identification of HCV-related cirrhosis, but lesser accuracy for earlier stages (Shaheen 2007).

All these tests are based on routine biochemistry blood assays and can be influenced by intercurrent conditions. At the same time, these scores may fluctuate or revert to lower classes after initial worsening and a dynamic overview is more valuable than a single determination.

In Europe, the typical approach is to perform a blood test such as one of the commercially available assays, followed by transient elastography. If both tests have concordant results on the disease stage, no biopsy is needed; if there is discordance, biopsy is performed. New fibrosis indexes combining the biochemical

scores and Fibroscan™ are being developed in order to provide a more accurate fibrosis stage classification (Boursier 2011).

Correlation between biochemical, histological and virological markers and HCV treatment

Patients should have serum transaminases (ALT and AST) levels monitored at one month, and then every 3 months, following initiation of therapy. Mild to moderate fluctuations in liver enzyme levels are common in persons with chronic HCV infection, and in the absence of signs and/or symptoms of liver disease they do not require interruption of antiviral therapy. Significant elevation in liver enzymes levels – more than 5 times the upper limit of normal – should prompt careful evaluation for liver insufficiency and for alternative causes of liver injury. Eventually, withdrawal of antiviral treatment may be required. A high baseline VL correlates with higher fibrosis and necrosis-inflammation scores (Mallet 2008). In patients with histologically proven cirrhosis without esophageal varices, successful treatment, as defined by a SVR, is associated with a reduction in decompensation, occurrence of HCC and mortality (Bruno 2007). The Child-Pugh (CP) classification of patients with HCV-induced cirrhosis is used in predicting the likelihood of SVR rate after antiviral therapy (AISF 2009):

- Patients with "histologically proven" cirrhosis without esophageal varices (Child class A5 to 6), identified by stages 5 and 6 of Ishak's score and stage 4 of the Metavir and Knodell scores. Presumed SVR rate is **25%** in HCV G1 and **75%** in non-G1 infected patients.
- Patients with "compensated" cirrhosis with or without esophageal varices (including Child class B7). Recognized SVR rate is **<15%** in HCV G1 and **<60%** in non-G1 infected patients.
- Patients with "decompensated" cirrhosis (Child class B8 or more) defined by any evidence of previous decompensation (ascites, esophageal bleeding, portal encephalopathy,

jaundice). Assumed SVR rate is **<7%** in HCV G1 and **<40%** in non-G1 infected patients.

The progression of fibrosis and other HCV-associated histopathologic changes may also be related to coagulation-cascade activity and hepatic accumulation of iron, which have been associated with mutations in factor V and hemochromatosis genes, respectively.

The HIV-HCV coinfection is a particularly challenging situation. The severity of liver disease must be routinely assessed in these patients in order to initiate treatment before progression of liver disease. An important number of coinfected patients are referred to hepatology clinics only when they have hepatic decompensation, at which time the HCV treatment options are limited.

Drug-induced liver injuries (DILI) following antiretroviral therapy pose significant problems in HIV/HCV co-infection, especially in persons with advanced liver disease and cirrhosis. Dose modifications or even avoidance of liver-metabolized antiretroviral drugs may be required in patients with CP class B and C disease. Overall, in the absence of clinically significant fibrosis, it seems worthwhile to defer treatment. However, it is equally important to apply the results of the clinical studies on a case by case basis, weighing the treatment response rate and the long-term outcomes.

Outlook

Nucleic acid testing, genotyping and assessment of the level of hepatic fibrosis are invaluable tools in the diagnosis of HCV infection, treatment guidance and monitoring.

Although LB is still considered the gold standard for the progression of hepatic fibrosis in chronic hepatitis C, a series of non-invasive radiological and serum-based markers are being investigated for their diagnostic accuracy. New real-time PCR tests are faster and more cost-effective methods for the

assessment viral kinetics. Virological end points are surrogate references for assessing the efficiency of HCV treatments, but many randomized trials on similar drug classes have established their value in correctly evaluating the clinical outcome. However, biochemical and histological improvements can be attained even in patients who fail to eradicate HCV infection. Obtaining data on the long-term clinical outcomes in patients included in previous treatment trials is logistically difficult, due to relatively high dropout rates and to interferences of re-treatment regimens. Cumulative meta-analysis may be relevant for the planning of future clinical trials.

Links

- **Centers for Disease Control and Prevention**. Guidelines for laboratory testing and result reporting of antibody to hepatitis C virus. MMWR Recomm Rep 2003;52(RR-3):1-13. http://www.ncbi.nlm.nih.gov/pubmed/12585742
- **World Health Organization.** Hepatitis C 2002. http://www.who.int/csr/disease/hepatitis/Hepc.pdf
- **Short guide to Hepatitis C.** By Mauss, Berg, Rockstroh, Sarrazin, Wedemeyer, et al. Flying Publisher 2011, 128 pages, www.goo.gl/7aTq4

3. Antiviral therapy in non-responders, relapsers and special populations

Liana Gheorghe and Speranța Iacob

More than 50% of genotype 1 and 20% of genotypes 2/3 HCV-infected patients fail to achieve a sustained virologic response (SVR) when treated with PegIFN/RBV. Non-sustained responders to PegIFN/RBV comprise a heterogeneous group of patients (non-responders, on-therapy and post-therapy relapsers) defined by the time point when they achieved or not undetectable viremia (see chapter 1). For these patients other therapeutic options are clearly needed.

How to manage genotype 1 non-responders and relapsers ?

Therapy selection: monitoring vs. retreatment

When considering further therapy for genotype 1 patients who fail to achieve a sustained viral response (SVR) during the initial standard-of-care (SoC) therapy, two important issues should be considered:

- the exact classification of the **initial response pattern** (as the response to subsequent therapy is strongly influenced by the initial response),

– the **correctable factors** of treatment failure during the previous course of therapy.

Consistent with the change in HCV RNA during the previous course of therapy, four different **patterns of treatment failure** – with crucial implications for the regimen, duration and likelihood of response to retreatment – can be distinguished:

1. Patients with less than 2 $\log_{10}$UI/ml decline in HCV RNA from baseline to treatment week 12 are defined as **non-responders.** Within this group, **null responders** show a minimal reduction in HCV RNA level (usually less than 1 $\log_{10}$UI/ml), being considered **the most refractory group to treatment with pegylated interferon alfa (PegIFN) and ribavirin (RBV)**. SVR rates during retreatment rarely surpass 15% in this population. Therefore, unless other compelling reasons impose therapy in these patients (such as control of extrahepatic manifestations or advanced liver disease), the best option may be to closely monitor them while waiting for triple therapy (PegIFN/RBV + a direct-acting antiviral).
2. Patients with ≥2 $\log_{10}$UI/ml decline in HCV RNA from baseline to treatment week 12, who remain HCV RNA detectable at week 24 are **partial virological responders.**
3. **Breakthrough** is defined as detectable HCV RNA during therapy, after an initial virologic response (HCV RNA undetectable or ≥2 $\log_{10}$UI/ml decline at week 12).
4. In contrast to previous categories, **relapsers** are those who, during therapy, achieved and maintained undetectable HCV RNA (measured by a high sensitive assay), but HCV RNA become again measurable during the first 6 months after the end of therapy. Relapsers have **the best chance of achieving SVR** during retreatment with PegIFN/RBV, with a SVR rate of approximately 40%. Triple therapy with a protease inhibitor further increase this rate.

Numerous host and virological factors strongly influence the response to therapy. A complex constellation of ***fixed factors*** related to *virus*, such as genotype 1 or high pre-therapeutic viral

load (VL) or to the *patient,* such as African-American or Hispanic race, severity of liver fibrosis/cirrhosis, hepatic steatosis or insulin resistance (IR), negatively impact the therapeutic outcome during a subsequent course of treatment. On the contrary, identifying ***correctable factors*** that may have contributed to prior treatment failure can help the decision of retreatment and subsequent management. The most common correctable factors that can significantly diminish the rate of SVR include:

Dose reduction, transient discontinuation or premature interruption of therapy, due to side effects such as anemia, neutropenia or depression. Close monitoring and judicious interventions (modest dose reduction, use of growth factors, prophylactic antidepressants) could minimize these factors.

Lack of adherence to the prescribed medication regimen. Rigorous adherence should be stressed and monitored.

Therapeutical strategies

The following strategies for prior genotype 1 non-responders and relapsers can be distinguished:

1. Retreatment with PegIFN/RBV
2. Extended treatment duration for slow virological responders
3. Increasing PegIFN dose and longer treatment duration
4. Optimizing PegIFN and RBV dosing during retreatment
5. Maintenance therapy with low-dose of PegIFN
6. Triple-combination therapy

1. Retreatment with the previous regimen (PegIFN/RBV). In the EPIC3 study, non-responders and relapsers to previous therapy with interferon alfa (n=1203) or PegIFN alfa-2a/2b (n=820) with or without RBV were retreated with PegIFN alfa-2b (1.5μg/kg/week) and weight-based RBV (800-1400 mg/day) for 48 weeks (Poynard 2009). **SVR was higher in prior relapsers vs. non-responders** (38% vs. 14%) and in patients who achieved

an EVR (56%) during the second course of therapy (Poynard 2008; Poynard 2009).

2. Extended treatment duration for slow virological responders. Slow virological responders are patients with ≥2 $\log_{10}$ decline in HCV RNA at treatment week 12, who achieve undetectable HCV RNA between 12 and 24 weeks of therapy. In this group, standard 48-week course of therapy has been associated with a high rate of virological relapse after therapy. Despite differences in study design (different criteria of randomization to extended therapy, different doses of RBV), several randomized controlled trials comparing 72 weeks to 48 weeks of treatment among slow virological responders have shown consistently that prolonged therapy significantly improves rates of SVR (44% vs. 28% [Sanchez-Tapias 2006]; 38% vs. 18% [Pearlman 2007]), largely by decreasing the rate of relapse (40% vs. 64% [Berg 2006]; 20% vs. 59% [Pearlman 2007]). However, **extending therapy has been associated with a higher rate of AEs and premature discontinuation** beyond 48 weeks of treatment, a finding that temper this approach in many patients.

3. Increasing PegIFN dose and longer treatment duration. Trials of **intensified regimen** with higher fixed-dose of PegIFN and/or longer treatment duration have demonstrated **only modest increases in SVR** in prior non-responders to PegIFN/RBV. In the REPEAT trial (Jensen 2009) prior non-responders received PegIFN alfa-2a higher-dose induction (360µg/week) for 12 weeks, followed by the usual 180µg/week for a further 60 or 36 weeks (total duration 72 and 48 weeks, respectively) with RBV 1000-1200 mg/day. The SVR rate was higher for those treated for 72 weeks; no difference was found between the induction and non-induction arms. This confirms that **retreatment of non-responders with extended therapy may improve SVR rates**, while **induction therapy with higher**

dose of PegIFN has no beneficial effect. Multiple logistic regression analysis indicated that EVR at 12 weeks consistently predicts SVR in retreated non-responders (Marcellin 2008).

4. Optimizing PegIFN and RBV dosing during retreatment. When combined with PegIFN, **RBV is critical to prevent relapse** after treatment cessation. A small prospective study on 10 patients with HCV genotype 1 infection and high baseline VL (>800, 000 IU/ml) showed feasibility and high efficacy of treatment with high RBV doses (Lindhal 2005). RBV was calculated to achieve a steady-state concentration above 15 µmol/ml. Prophylactic and as-needed administration of erythropoietin and blood transfusions were required in a single patient. SVR was achieved in 9 of 10 patients without major treatment regimen violation. RBV dosing at 13-15 mg/kg appears to be the best balance between optimized efficacy and intolerable hemolytic anemia that develops at high doses. SVR is significantly diminished when RBV dose is below 11 mg/kg. Therefore, maximizing RBV dosing, particularly in overweight patients, has the potential to improve SVR during the second course of therapy. In a retrospective analysis of a large database of patients treated with PegIFN/RBV, it has been demonstrated that RBV dose reduction led to a stepwise decrease in SVR. The cumulative dose of RBV below 60% is associated with an evident decline in SVR (Reddy 2007). Thus, not only **maximizing RBV dosing**, but also **maintaining a cumulative RBV dose higher than 80% of the overall dose**, with or without erythropoietin, **improves SVR** in previous non-responders and relapsers. Other trials (Fried 2006) demonstrated improved SVR in patients with body weight above 85 kg treated with higher dose of PegIFN/RBV. Patients treated with PegIFN alfa-2a, 270 µg/week and RBV 1600 mg/day, showed an SVR of 48% versus 28% in those treated with standard dosing regimen (relapse rates 19% vs. 40%). However, **higher dose regimen** was associated with a**n increased rate of hematological AEs**.

5. Maintenance therapy with low-dose of PegIFN. Non-sustained responders to SoC, with advanced fibrosis or cirrhosis, have a high risk for disease progression and complications. Two large multicentre trials have evaluated the benefits of maintenance therapy with low-dose PegIFN in this group:

- the COPILOT study (Colchicine vs. PegIFN alfa-2b 0.5 µg/kg/week Long Term) (Afdhal 2008)
- the HALT-C study (Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis with PegIFN alfa-2a 90 µg/week) (Di Bisceglie 2008)

In the COPILOT study 555 patients with prior failure to interferon-based therapy were randomized to receive either PegIFN alfa-2b 0.5 µg/kg/week (n=286) or colchicine 0,6 mg twice daily (n=269). No differences were observed between the two groups with respect to progression of the CP score, development of complications of portal hypertension or HCC.
The HALT-C trial was a prospective, randomized, controlled study of long-term maintenance therapy with PegIFN alfa-2a 90 µg/week (n=517) or no treatment (n=533) for 3.5 years in patients with chronic hepatitis C (CHC) and advanced fibrosis or cirrhosis (Ishak score 3-6) who did not achieve SVR after interferon-based therapy. By the end of the study period, there was no difference between the control and treated groups in the frequency of death, hepatic decompensation or development of HCC. Overall, the COPILOT and HALT-C trials showed that **maintenance therapy with low-dose PegIFN alfa-2a or alfa-2b does not reduce the rate of liver-related death, clinical disease progression and complications** over a period of up to 4 years.

6. Triple-combination therapy. Triple therapy combination of PegIFN/RBV with a protease inhibitors (telaprevir or boceprevir) in HCV genotype 1-experienced patients has been shown to produce high rates of virological response in both prior relapsers

and, to a lesser extent, prior non-responders in phase III trials. A detailed presentation of the newly aproved direct-acting antivirals (DAAs) is given in chapter 4.

Prove-3 trial evaluated triple-combination therapy with **telaprevir** in treatment-experienced patients (~60% non-responders and ~40% relapsers) (McHutchison 2010). Patients were randomized on four treatment arms in order to assess the impact of different durations of triple therapy, different total treatment duration and the importance of RBV for this difficult-to-treat population. Prior relapsers treated with 24 weeks of triple therapy followed by 24 weeks of PegIFN/RBV (total duration of therapy 48 weeks) had a SVR rate of 76%, while prior non-responders had lower rates of SVR (~40%).

RESPOND-2 evaluated triple therapy combination with **boceprevir** in non-responders and relapsers (Bacon 2011). The results indicate that 75% of prior relapsers and 52% of prior non-responders treated with a fixed triple therapy boceprevir regimen achieved SVR. In the response-guided arm, SVR was 69% in prior relapsers and 40% in prior non-responders.

Curent available data clearly show that that t**riple therapies including a protease inhibitor provide higher chance of SVR for relapsers and non-responders**. The benefits of these novel treatment regimens for each individual patient must be weighed against the side effects, costs and potential of developing viral resistance.

Practical approach to retreatment

When deciding retreatment of previous non-sustained responders to standard therapy, the following practical issues should be considered:

- **Patient's motivation** for another course of therapy. Lower likelihood of SVR in treatment-experienced patients, side effects, poor QoL should be discussed with the patient;
- **Severity of liver disease** (clinical, biochemical, histological). Patients with minimal-to-moderate fibrosis

may wait for triple therapy while patients with advanced fibrosis should be treated immediately with available regimens;
- **Virological response** during the initial course of therapy. Null and partial responders achieve lower SVR rates as compared with relapsers, irrespective of therapeutic regimen. Slow virological responders who have relapsed may benefit from extending duration of therapy;
- **Previous dose regimen and adherence assessment**. Optimizing RBV dosing, minimizing dose reductions by use of growth factors and avoiding premature discontinuations are important issues during retreatment;
- **Correctable factors** that may affect the subsequent response to therapy: steatosis, insulin-resistance, chronic alcohol consumption etc.

How to manage genotype 2 and 3 non-responders and relapsers ?

Nonresponders/relapsers infected with HCV G2/3

Genotype 2 or 3 infected patients are easier to treat and require only 24 weeks of therapy with PegIFN and low-dose of RBV (800 mg/day) (Zeuzem 2004). Patients who are intolerant of a planned 24-week course of therapy can discontinue the antiviral therapy between weeks 12 and 16 without a negative impact on SVR, if they have achieved a RVR (Mangia 2005).

Treatment failure is uncommon in genotype 2 and 3 patients. Primary non-response to PegIFN/RBV is a very rare event, while partial response or virological relapse after therapy withdrawal may be detected in a subgroup of patients. Factors that have been associated with suboptimal response to SoC in HCV genotypes 2/3 patients include hepatic steatosis, obesity and IR (Zeuzem 2004, Poustchi 2008), advanced fibrosis (Dalgard 2004) and high pretreatment viremia (Shiffman 2007).

In most clinical trials, SVR rates in patients with HCV genotype 2 or 3 chronic infection, considered as a single group, exceed 80%

(Zeuzem 2008). However, in a meta-analysis (Andriulli 2008), an overall SVR rate of 80-89% for HCV genotype 2, but only 66-80% for genotype 3 was reported, with an estimated 8.7% difference in SVR rates between the two genotypes after a 24-week course of PegIFN alfa-2b plus RBV. Reduced response in genotype 3 is associated with a higher incidence and degree of steatosis and higher rate of post-treatment relapse.

Retreatment of HCV genotype 2 and 3 patients

Retreatment with PegIFN/RBV for 48-52 weeks in genotype 2 or 3 patients, who have failed previous therapy, can achieve SVR in more than 60% of previous relapsers and in more than 30% of previous non-responders (Zeuzem 2008, Shiffman 2007). On the basis of these findings, **retreatment with a 48-52 week course of PegIFN/RBV is clearly recommended in genotypes 2/3 relapsers, partial responders or non-responders** to the previous 24-weeks course of SoC.

Recently, it has been suggested that patients with genotype 3 HCV infection and advanced liver fibrosis or cirrhosis should be treated from the very beginning for at least 48 weeks, based on the observation than many of them relapse after therapy discontinuation when treated for only 24 weeks (Mangia 2009).

Despite the fact that most DAAs against HCV have been designed to target patients with genotype 1 infection (the largest pool of patients who fail to respond to currently available therapies), some of these new compounds may be active also on non-1 genotypes. For example, telaprevir and other investigational protease inhibitors (for details, see chapter 4) have been recently shown to have significant antiviral activity against genotype 2, but not genotype 3.

Special categories of patients

Given the increased prevalence of HCV infection among special populations there is a stringent need to broaden the spectrum of patients eligible for therapy.

Injecting drug users (IDUs)

CHC is hyperendemic among IDUs. There are several challenging aspects that have to be considered before effective antiviral therapy can be provided to this group of patients (Roy 2002):

- uptake of antiviral therapy is low in these patients, depending on the phase of addiction (active/regular IDUs, on maintenance therapy with methadone; past users; abstinence)
- adherence to therapy is low
- side effects are frequent and difficult to manage in the context of drug dependency
- there is a risk of relapse to drug use in patients who are currently abstinent or on maintenance therapy even after HCV therapy is started
- even after successful HCV eradication, there is a high risk of reinfection in IDUs (Backmund 2001)

When treatment is indicated in IDUs, it should be provided as soon as possible and during any phase of drug addiction, with the same regimen (dose, duration) delivered to the non-drug users. Treatment uptake and adherence to therapy is usually low in active IDU and reinfection may occur. Treatment should preferably be postponed until the patient is stabilized on maintenance (methadone) therapy. Treatment of abstinent/past users is associated with excellent adherence, being as effective as in non-drug users (Wilkinson 2009). Psychiatric illnesses are common among IDU and high awareness and early intervention for psychiatric side effects during HCV treatment is important.

Hemodialysis patients

Due to the early nosocomial spread of HCV within hemodialysis units (Fabrizi 2007), the infection is highly prevalent in this setting and the treatment of CHC in this population remains a challenge to clinicians.

A meta-analysis on the impact of HCV infection on mortality in the dialysis population (seven observational studies enrolling 11,589 subjects on maintenance hemodialysis) showed a detrimental impact of HCV on survival in patients with chronic kidney disease (Fabrizi 2008). Positive anti-HCV serological status after kidney transplantation is implicated in the pathogenesis of acute glomerulopathy, "de novo" graft-associated nephropathy, new-onset diabetes mellitus, and increased incidence of infections.

There are good data to support antiviral therapy in the pretransplant patients (see chapter 5). The decision to treat such a difficult subgroup of patients should be based on liver histology, age, comorbidities, and ability to tolerate therapy. In a meta-analysis of patients on maintenance hemodialysis, the overall SVR was 37% in the whole group and 30% in patients with HCV genotype 1 (Fabrizi 2008). The viral response to monotherapy with standard interferon in maintenance hemodialysis patients is higher than that observed in patients with CHC and normal kidney function (7-16%), due to the following factors: lower VL, milder histological forms of liver injury, a decreased interferon clearance, and an increase in endogenous interferon release from circulating white blood cells during hemodialysis procedures.

Data on PegIFN monotherapy and PegIFN/RBV therapy in hemodialysed patients are limited. Very low amounts of RBV are removed via dialysis, leading to drug accumulation and exacerbating hemolysis in this population, already at significant risk for anemia. Therefore, the decision to use combination therapy in hemodialysed patients should take into consideration several precautions: 1) use of very low RBV doses (200 mg x

3/week), 2) weekly monitoring of hemoglobin levels, and 3) use of high erythropoietin doses to treat anemia (Bruchfeld 2006).

Patients with psychiatric comorbidities

A prevalence of 60% psychiatric comorbidities has been reported in patients with CHC. On the other side, neuropsychiatric side effects occur in up to 50% of patients receiving treatment with PegIFN/RBV, the commonest being depression. Prospective clinical trials suggest that patients with HCV infection and psychiatric comorbidities can be safely treated with interferon-based antiviral regimens by both hepatologists and mental health professionals as part of a multidisciplinary team (Knott 2006). An expert psychiatric assessment is required before the decision about the management of HCV infection in this group of patients. Through close collaboration between hepatologist and psychiatrist, a significant proportion of patients with CHC and well controlled psychiatric comorbidity can safely and effectively receive antiviral treatment.

Patients with inherited anemias

CHC is common in patients with thalassemia major or sickle cell disease, as a result of regular or intermittent red blood transfusions. In addition to HCV injury, progression of liver fibrosis is influenced by the degree of hepatic iron overload, with high rates of cirrhosis and hepatocellular carcinoma (Angelucci 2002). With PegIFN/RBV combination, SVR has been reported in 40-70% of patients with thalassemia. Patients with thalassemia major are at increased risk of AEs of interferon and careful monitoring for side effects, iron chelation (with liver iron maintained between 2-7 mg/g dry weight), and regular transfusions may be necessary. These patients should be managed preferably by a hepatologist and a hematologist, in a joint clinic.

African Americans

CHC in African Americans shows a more favorable course characterized by lower serum ALT level, less inflammation on biopsies, less trend to progress to cirrhosis, but a greater than threefold higher risk of HCC as compared with whites.
African Americans have lower SVR when treated with PegIFN/RBV (Jeffers 2004). In WIN-R trial, African Americans have a significant higher SVR when treated with PegIFN alfa-2b and weight-based RBV doses ranging between 800 and 1400 mg/day as compared with fixed RBV dose of 800 mg/day (21% vs. 10%, p=0.004) (Jacobson 2004). Despite advances in HCV therapy, African Americans have decreased SVR with PegIFN/RBV, even when optimized dosing is used and this may be explained partly by the high distribution of unfavorable genetic predictors of SVR (such as genotype 1 (McHutchison 2000) and unfavorable allele CT and TT of IL28B (Ge 2009) as compared with other ethnic groups (see also chapter 1).

HIV-HCV coinfection

Because of shared risk factors, HCV co-infection is common (10-40%) among HIV-infected persons. HIV infection accelerates the progression to advanced fibrosis and cirrhosis and increases the risk for liver-related complications, including hepatocellular carcinoma compared with HCV monoinfected patients. As a result of the effectiveness of highly active antiretroviral (HAART) therapy, the longevity of HIV-infected patients has increased and HCV infection emerged as a major cause of morbidity and mortality among this population.
A significant proportion of HIV-HCV coinfected patients (with stable HIV infection, no AIDS, mean CD4 counts greater than $400x10^6$/L and compensated liver disease) can be treated successfully with PegIFN/RBV. SVR to PegIFN/RBV is lower in HIV-HCV coinfected patients, ranging between 26% and 44% (Torriani 2004, Carrat 2004).

Several trials recommended 48 weeks of PegIFN/RBV in co-infected patients, regardless of HCV genotype (Iorio 2010). The SVR in HIV-HCV infected patients can be predicted by the so called "Prometheus index" that associates HCV genotype, degree of fibrosis, HCV VL, IL28B genotype (Medrano 2010).

Safety, tolerability and adherence to combination therapy are important issues in the coinfected patients, with 12% to 42% discontinuation rates. HAART can be associated with anemia, thrombocytopenia, neutropenia and hepatotoxicity, ranging from elevation in aminotransferases level to hepatic decompensation and mitochondrial toxicity (i.e., acute pancreatitis and lactic acidosis which occur especially in patients receiving didanosine).

Autoantibody (ANA, ASMA, anti-LKM) seropositivity in the setting of CHC is common, but does not impact on disease progression, nor on response to antiviral therapy. It is important to recognize an autoimmune component (high autoantibody titer ANA>1:160 or ASMA>1:80, elevated liver enzymes (more than 5-10 times UNL and specific features on LB) before starting therapy, as PegIFN-based regimens may exacerbate underlying autoimmune hepatitis. If immunosuppression for autoimmune component is required, aminotransferases should be followed closely during the first weeks of therapy.

Obesity and metabolic syndrome are common in patients with CHC and associated with lower probability of achieving SVR with antiviral therapy. Insulin resistance is one mechanism by which response to antiviral therapy is reduced. Interventions targeting at reducing obesity or/and IR may improve SVR rates. It is important to stress that body weight-adjusted dosing regimens improve rates of SVR.

Outlook

A large proportion of patients with genotype 1 CHC will not respond to standard of care treatment (SoC). Patients with treatment failure to PegIFN can be classified into null responders, partial responders, patients with breakthrough and relapsers. Multiple fixed and correctable factors identified during the previous course of treatment must be considered when counseling about retreatment. The kinetic in HCV RNA during a prior course of therapy has important implications for the likelihood of response to retreatment. Triple combination regimens including a protease inhibitor, such as telaprevir or boceprevir, proved to be a good option for prior non-sustained responders.

Treatment failure is uncommon in patients with genotypes 2/3 HCV infection. Retreatment in these patients should be considered, as response rates are reasonable, particularly with prolonged duration of therapy.

There is an increased prevalence of HCV infection among special populations (IDUs, comorbidities, HIV-infected patients, African Americans) and their management requires special consideration.

Links

- International clinical trials registry platform: http://www.who.int/ictrp/en
- US clinical trials registry: http://clinicaltrials.gov
- Cochrane Database of Systematic Reviews
- http://www2.cochrane.org/reviews
- HCV Drug Dose and Response Decision Support Tool – Clinical Care Options http://www.clinicaloptions.com/Hepatitis/Management
- Nature Reviews Gastroenterology & Hepatology http://www.nature.com/nrgastro/journal/v8/n5/index

4. Searching for new antiviral therapies

Simona Ruta and Costin Cernescu

Candidates for new therapeutic approaches

The current Standard of Care (SoC) combination therapy for chronic hepatitis C (CHC) is limited by its insufficient efficacy in some patient groups, the drug side-effects and contraindications and the high associated costs. There are an increasing number of therapeutic failures, with patients who do not respond or who relapse with the available SoC. Assuming there are no changes in the type of treatment, the projection for the next 20 years is that the total number of patients with advanced liver disease will be 4-fold higher than today, with nonresponders far exceeding those actively treated and total medical costs being expected to triple.

New therapeutic approaches will be especially important for

- **Patients with significant adverse events (AEs)** associated with SoC therapy. In clinical trials, AEs imposed dose-reduction in more than 60% of the cases and treatment withdrawal in 10–15% of cases; in clinical practice, the rate of treatment discontinuation is substantially higher.
- **Treatment-naive and challenging populations.** These include patients infected with viral genotypes 1 and 4 (which are refractory to the current SoC), especially those

with unfavorable pre-treatment characteristics (high VL, advanced fibrosis, IL28B unfavorable genotypes CT or TT), as well as other "difficult-to-treat" populations detailed in chapter 3.
- **Relapsers and nonresponders of all genotypes.**

Different treatment options that can either augment the efficacy of current therapy or potentially result in PegIFN- and/or ribavirin (RBV)-sparing regimens are being extensively studied. New emerging therapies include
- improved interferon (IFN) alfa formulations (to enhance efficacy and ease of administration)
- alternative RBV-like molecules (to reduce toxicity)
- direct-acting antivirals (DAAs) that target specific key steps of the viral life cycle

New IFN formulations

New interferons are currently being developed to offer enhanced activity, improved AE profiles and, hopefully, better tolerability compared with currently available ones (Table 4.1). Given the dependence of treatment success on patients adherence, the development of longer-acting IFN formulations, with improved pharmacokinetic profiles, is an important focus of HCV therapy. Their main advantages consist in maintenance of viral suppression across a longer dosing interval, avoidance of inter-dose trough, and reduced dosing frequencies (twice or even once per month compared to once per week for the current pegylated interferons (PegIFNs). Although studies about improved formulations of interferons have been focused on HCV genotype 1, their administration can be also valuable for genotype 2 or 3 infected patients. In easy-to-treat patients (infected with genotype 2 or 3), the duration of treatment can be reduced to 12 weeks if a rapid virologic response (RVR) is obtained. This can translate into a very convenient therapeutic regimen of only 3 injections, if longer-acting IFNs, with monthly dosing, are going to be used.

However, not all patients may benefit from these new types of IFNs. In particular, it seems unlikely that patients with strong contraindications to the current IFNs will be eligible for treatment with newer formulations, even if the AEs profiles of the new IFNs are milder.

Table 4.1 – New interferons in the treatment of Chronic Hepatitis C*

Interferons/ Manufacturer	Description	Clinical trial phase
Interferon alfacon (consensus interferon- INFERGEN®) Three Rivers Pharmaceuticals www.3riverspharma.com	Bio-engineered IFN, consisting of the most frequently observed amino acid in each corresponding position in the natural alfa IFN	approved
IFN formulations with improved pharmacokinetic profiles		
Albinterferon (Zalbin™) Human Genome Sciences www.hgsi.com	Recombinant IFN alfa-2b fused with human albumin	III
IFN preparations with improved side-effect profiles		
Pegylated Interferon lambda Zymogenetics/Bristol-Myers Squibb www.zymogenetics.com	Type III interferon with restricted receptor distribution (especially on hepatocytes)	II
Controlled-release recombinant interferon systems		
Locteron® BiolexTherapeutics www.octoplus.nl	Recombinant IFN alfa-2b in polyetherester microspheres	II
Interferon alfa-2b XL Flamel Technologies www.flamel.com	Recombinant IFN alfa-2b with Medusa® nanoparticles delivery system	II
Omega Interferon Intarcia Therapeutics www.intarcia.com	Delivered with Omega DUROS®- continuous micropump infusion system	II

* According to data from: Hepatitis C new drug pipeline (http://www.hcvdrugs.com, accessed on 4/29/2011); low dose oral interferon (Amarillo Bioscience) and oral Belerofon (Nautilus) are not included.

Interferon alfacon or consensus interferon (CIFN) (Infergen®, Three Rivers Pharmaceuticals) is a recombinant, bio-engineered interferon, consisting of the most frequently observed amino acid in each corresponding position in the natural alfa IFN. It

shares an 89%, 30% and 60% homology with IFN alfa, IFN beta and IFN omega, respectively. The CIFN molecule binds to the IFN-alfa receptor with higher affinity than all other known IFN alfa molecules (including the natural subtypes, the variants or recombinants). *In vitro* it appears to be approximately 5 to 20-fold more active than PegIFN alfa-2a and alfa-2b (Gonzalez 2009).

Data derived from clinical trials support the use of CIFN for treatment-naive patients, particularly those with high VL or genotype 1 infection (Sjogren 2005), as well as in the retreatment of relapsers and nonresponders (Leevy 2008).

Clinical trials suggested a dose-dependent rate of viral clearance, however the maximum tolerated dose of daily CIFN in difficult-to-treat patients is up to 15 μg/day (Bacon 2009). Administration of an induction dose (up to 18μg/day) or of a higher dose (24μg/day), did not translate to better rates of SVRs and was associated with more serious AEs and more discontinuations (Meyer 2010).

CIFN is approved as monotherapy for CHC in adults with compensated liver disease, and, from 2010, for retreatment of CHC, in combination with RBV, being especially effective for interferon-sensitive patients with lower baseline fibrosis scores.

IFN lambda (IFN-λ) is a type III interferon (comprising of IL28A, IL28B and IL29), which has previously demonstrated strong antiviral activity and good tolerability. IFN-λ mediates antiviral activity through a different signaling pathway than type I interferons (such as IFN alfa), having a complex binding mainly through the IL28 receptor, which is present only on plasmacytoid dendritic cells, peripheral B cell, hepatocytes and epithelial cells. This restricted distribution compared to that of IFN-alfa receptor offers the potential for more targeted hepatic delivery, as well as for a better tolerability and safety profile than the conventional interferons in terms of bone marrow suppression (Sommereyns 2008). IFN-λ can enhance the sub-saturating levels of IFN-α and increase its antiviral efficacy. As a result, the combination of IFNλ and IFN-α may provide additive

therapeutic effects through the complementary roles of the two types of cytokines (Pagliaccetti 2008). IFN-λ may be used to target specific cell responses and to avoid the AEs of IFN-αs. **Interferon lambda** has been **pegylated** (Zymogenetics/Bristol-Myers Squibb); its administration in treatment-naive patients chronically infected with HCV genotypes 1/2/3/4 resulted in higher rates of RVR and EVR, which extended across all IL28B host genotypes, and was associated with fewer hematologic toxicities, flu-like and musculoskeletal symptoms compared with PegIFNα-2a (Zeuzem 2011). IFN lambda might prove to be increasingly important for the treatment of CHC, due to the recent findings (see chapter 1) on the impact of host genetics in the response to therapy (Tanaka 2010).

Albinterferon (Zalbin™, Human Genome Sciences) is a longer-acting IFN, allowing for once or twice/month dosing schedule. It consists of IFN alfa-2b genetically fused to recombinant human albumin. Several unique features of albumin make it an ideal candidate for integration into a drug-design platform, including its unusually long half-life (~19 days), wide distribution, negligible potential for confounding enzymatic or immunological function and its physiological role as a carrier of blood substances. The pharmacodynamic attributes of albinterferon, which include the maintenance of viral suppression across a longer dosing interval, might reduce viral rebounds, while also improving patient's compliance.

In phase III trials, in patients with genotype 1 CHC, albinterferon (900 μg every 2 weeks) achieved noninferiority compared with PegIFN alfa-2a, indicating that the two drugs are equivalent (Nelson 2009). Albinterferon was also administered with good results in combination with RBV in non-responders to prior IFN therapy and is evaluated for the treatment of HIV/HCV coinfected patients. However, the preliminary FDA evaluation indicates that the licensing of this dosing regimen is unlikely, due to the unfavorable risk-benefit profile, mainly caused by slightly increased rates of serious pulmonary AEs, coughing and

alopecia compared to PegIFN. Development and testing of once per month dosage is undergoing.

Controlled-release recombinant interferon alfa-2b formulations were designed to improve the pharmacokinetic parameters, in order to maintain continuous drug levels and consequently minimize side effects as compared to current IFNs.

Locteron® (Biolex Therapeutics/OctoPlus) is a recombinant nonglycosylate IFN alfa-2b produced in polyether-ester microspheres. This steady controlled-release formulation avoids fluctuation in IFN levels. A pilot study reported that after injection of 320 μg Locteron®, the concentration of serum IFN remained elevated through 14 days (De Leede 2008). Locteron® can be administered twice monthly, with its trough concentration between doses maintaining adequate antiviral activity. Preliminary results of phase IIb studies, showed that in treatment-naive patients, Locteron®, in combination with RBV, produced similar viral suppression to that of PegIFN/RBV, with fewer flu-like side effects and substantially lower rates of depression.

IFN XL (Flamel Technologies) is an extra-long controlled-release formulation of recombinant IFN alfa-2b, based on the nanoparticles **Medusa delivery system**, designed for the tailored delivery of fully-active proteins. Basically this is a nanoparticle polymer with embedded IFN, which has a slow, sustained release with increased efficacy. In a phase I study, IFN XL induced greater reduction in VL after two weeks with fewer AEs compared to PegIFN (Soriano 2009). A phase IIa study designed to evaluate IFN XL in combination with RBV in naive and previous G1 HCV non-responders to SoC is ongoing.

Omega interferon (Intarcia Therapeutics, Inc.) is a type 1 interferon delivered with an osmotic mini-pump implanted subcutaneously. Omega DUROS® is a drug delivery system that stabilizes therapeutic proteins, delivering a continuous dose of omega interferon at a constant rate for 3 months.

Alternative RBV formulation

Optimal RBV dosages are essential in achieving a SVR. Maintenance of RBV in the therapeutic regimen has been proven to have an important additive effect in the overall success rate, leading to both increased RVR and reduced rates of relapses (as demonstrated by the PROVE-2 trial).

As described in chapter 1, the main impediment in the administration of high-dose RBV is the dose-dependent development of hemolytic anemia. Although the addition of epoetin alfa has been useful in maintaining the highest possible RBV doses, new RBV-replacement compounds, with an improved side effects profile, are investigated.

Taribavirin – formerly known as viramidine – (Valeant Pharmaceuticals International/Kadmon Pharmaceuticals LLC), is a prodrug of RBV, converted in the active form by adenosine deaminase. This nucleoside analog was studied for the treatment of CHC, due to the lower frequency of anemia, a benefit registered especially within the first 12 weeks of treatment, the period in which maintenance of the dose of RBV has been shown to be the most critical. The major conversion site of taribavirin is in the liver, enabling drug concentration in this location. Due to its lower uptake in red blood cells, taribavirin causes significantly less hemolytic anemia compared to RBV. While this effect was confirmed in several clinical studies, the rates of SVR were lower with taribavirin.

In two phase III studies, taribavirin failed to prove noninferiority compared to RBV (SVR rates were 38% and 40% with taribavirin vs. 52% and 55% with RBV in the VISER 1 and VISER 2 trials, respectively), even if taribavirin caused lower rates of severe anemia (5% vs 24%). Suboptimal dosing of taribavirin (Marcellin 2010) seems to be the explanation, as recent studies with weight-based dosing of taribavirin confirmed reduced rates of anemia (7%-15% vs. 24% with RBV), while acquiring comparable SVR rates and lower relapse rates than RBV. Whether taribavirin will have a role in the future

combination therapies including DAAs (most of which are also associated with a certain degree of anemia) remains to be seen.

Direct-Acting Antivirals (DAAs)

Direct-acting antivirals (DAAs), also known as "specifically targeted antiviral therapy for hepatitis C" (STAT-C), are the most important new therapeutical options for CHC. In May 2011, two HCV protease inhibitors Telaprevir (Incivek™) and Boceprevir (Victrelis™) have been approved by the FDA. For the first time, we have now drugs with specific anti-HCV activity. Several other DAAs are at various stages of clinical development, the most advanced being alternative protease inhibitors and nucleoside and non-nucleoside polymerase inhibitors. Other tentative approaches include inhibitors of host cyclophilins, alpha-glucosidase inhibitors, oligonucleotides and immune modulators (Soriano 2009).

Protease inhibitors (PIs)

A clear understanding of the key sites of action for the newer antiviral compounds in development is of outmost importance. HCV is a positive-sense single-stranded RNA virus, meaning that its genome can function directly as a template for viral protein synthesis. Consequently, after entering into hepatocytes, HCV starts its replication by direct translation of the genome into a large polypeptide that is further processed by the virus NS3 protease. This enzyme has dual activity of serine protease and of helicase (unwinding the single-strand viral RNA). Together with the NS4A cofactor, the NS3 protease is responsible for proteolytic cleavage of its downstream nonstructural proteins that in turn are critical in forming the replicative complex from which viral synthesis occurs. Additionally, NS3 protease may directly impair host IFN responses through the inhibition of phosphorylation of IFN regulatory factor-3, and administration of PIs may restore interferon responsiveness.

Both FDA-approved PIs – Telaprevir and Boceprevir – are peptidomimetic PIs that bind reversibly and block the protease catalytic site.

However, **monotherapy with PIs is not an option**, due to early emergence of resistance. Minor resistant populations preexist at baseline in all HCV-infected patients and are rapidly selected with PIs monotherapy. Therefore, boceprevir and telaprevir still **require a platform of PegIFN/RBV**. When administered in this triple therapy combination, each of the two PIs substantially increases the rates of SVR in both treatment-naive and treatment-experienced patients.

Triple therapy

Triple therapy with a PI was shown to almost double the success rate in treatment-naive patients infected with HCV genotype 1 from 38-44% obtained with SoC to 63-75% (Poordad 2011). The increase in SVR rate is even higher in previous nonresponders-from 17-21% with SoC to 59-66% with triple therapy (Bacon 2011). Nevertheless, the addition of a new agent to an existing treatment regimen will pose substantial challenges in terms of drug interactions and adherence, due to the associated side effects and risk of resistance emergence. Maximizing tolerance of future PIs based regimens will be extremely important to achieve optimal treatment outcomes.

Telaprevir (Incivek™, Vertex Pharmaceuticals) was approved by FDA for treatment of genotype 1 CHC in adult naive patients with compensated liver disease, including cirrhosis, and in prior null responders, partial responders, and relapsers, only in combination with PegIFN/RBV.

Preliminary studies have demonstrated that 14 days monotherapy, while inducing a VL median decline of more than 4.4 $\log_{10}$ units in patients with CHC G1 infection, was limited by the appearance of resistance mutation as early as 4-7 days after initiation. Interestingly, the mutations were subsequently suppressed by administration of PegIFN/RBV. Consequently, telaprevir was administered in combination with PegIFN/RBV

for 12 weeks, followed by SoC therapy alone for another 24 - 48 weeks. The recommended dose of Incivek is 750 mg orally 3 times a day.

Several phase II and III studies have assessed the efficacy and safety of telaprevir in treatment naive G1 patients, concluding that triple therapy yields a higher rate of SVR than current SoC and lower rates of relapse. The SVR for patients treated with Incivek across all studies, and across all patient groups, was between 20 and 45% higher than the current SoC (Hézode 2009, McHutchison 2009). RBV was shown to be an essential part of the therapeutic regimen, playing a critical role both in achieving superior RVR and SVR and in reducing the rates of virologic breakthrough due to drug resistance.

The results of a response-guided therapy (RGT) study, ILLUMINATE (Sherman 2010) support a shorter course of treatment (from 48 to 24 weeks) for rapidly responsive naive-patients. Sixty percent of previously untreated patients achieved an EVR and received only 24 weeks of treatment. The SVR for these patients was 90%. In order to identify patients who may benefit from shorter duration of therapy, a new predictor of treatment response was proposed: extended RVR (eRVR), defined as undetectable HCV RNA at week 4 and 12. Among patients who achieved an eRVR, rates of SVR were comparable between those treated for a total duration of 24 or 48 weeks (92% vs. 88%, respectively). Among those who did not achieve eRVR, but continued treatment for 48 weeks, the SVR rate was lower, but still significant (64%). More recent studies have evaluated the use of triple therapy including telaprevir as a retreatment option for nonresponders and relapsers to previous SoC therapy, demonstrating synergistic effects in viral reduction and decreased emergence of resistance. SVR rates were higher among patients who previously experienced relapse versus nonresponders (McHutchison 2010).

Rashes, pruritus, anemia and nausea were the most commonly reported AEs with the use of telaprevir. AEs rates resulting in treatment withdrawal were about 10% higher in telaprevir arms

vs PegIFN/RBV, the most severe being rash, that resolved with discontinuation of therapy. Serious skin reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson Syndrome were reported in less than 1% of subjects who received telaprevir combination treatment compared to none who received PegIFN/RBV alone. A sequential discontinuation of drugs was proposed for the management of moderate or severe rash.

Boceprevir (Victrelis™, Merck) is another potent HCV NS3 PI with antiviral activity against genotype 1 HCV. Boceprevir is FDA approved for the treatment of CHC genotype 1 infection, in combination with PegIFN/RBV, in patients aged 18 years of age and older with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy. Boceprevir is administered orally, at a dose of 800 mg three times daily.

The safety and efficacy of triple therapy with oral boceprevir plus PegIFN/RBV vs PegIFN/RBV alone were demonstrated in a phase III registration trial for treatment-naive patients, SPRINT-2 (Poordad 2011) and in previously partial responders and relapsers to SoC (RESPOND-2) (Bacon 2011). Boceprevir, in combination with PegIFN/RBV has not been studied in patients documented to be historical null responders (less than 2 $\log_{10}$ HCV RNA decline by treatment week 12) during prior therapy with PegIFN/RBV.

The treatment strategy is different from telaprevir, Boceprevir being administered in triple combination therapy for 24-44 weeks only after a 4 weeks lead-in phase with PegIFN/RBV alone. Therefore, RVR was defined as undetectable HCV RNA at week 4 of boceprevir-containing therapy (meaning week 8 of all therapy, including the lead-in period). In theory, a lead-in phase may provide the additional advantage of reducing viral replication and, consequently, the rate of resistance emergence. However in phase III clinical trials, patients with poor response to PegIFN/RBV, defined as <1 $\log_{10}$ decline after 4 weeks lead-in, had a higher incidence of resistance mutations. Nevertheless, the

virologic response at the end of the lead-in phase is highly predictive for the final outcome of therapy. Substantially higher SVR rates are obtained in patients showing more than 1 $\log_{10}$ decline in HCV RNA at this time point. Even in patients with a poor response to interferon, addition of boceprevir can generate a SVR in up to 34% of the patients. This is an important information, arguing for the utility of a lead-in phase in the previously treated nonresponders or relapsers. For naive patients, the lead-in period can further serve to test both compliance and tolerability before exposure to PIs.

The most commonly reported AEs with boceprevir were anemia (almost twice as many boceprevir recipients had Hb levels <9.5 mg/ml compared to controls) and dysgeusia (more than twice as often in boceprevir recipients than in controls). Serious AEs were reported in 11% of patients receiving boceprevir in combination with PegIFN/RBV compared with 8% of patients receiving PegIFN/RBV alone. The most common reason for dose reduction in the trials was anemia.

Other investigational HCV PIs

A series of additional PIs are in development and preliminary studies confirm their superior antiviral effectiveness in combined triple therapy over the SoC in treatment-naive patients. Unlike telaprevir or boceprevir, which are active only on genotypes 1 and 2 and have to be dosed three times a day, investigational second-generation PIs, mainly non-covalent inhibitors of the NS3/4A, seem to be active against different HCV genotypes, as well as against resistant HCV variants previously selected by other PIs. Also, they have a longer half-life which enables more convenient once-daily dosing. In addition, they may provide improved safety and efficacy as well as shortened treatment duration for a higher proportion of patients. An example is **BI 201335,** a once-daily HCV NS3/4A protease inhibitor optimised to target genotype-1 HCV, with strong in vitro activity also against GTs 4-6. Phase II studies showed BI 201335 to have strong efficacy, with overall SVR rates

reaching 83% in GT1 patients at once-daily dosages of 240 mg (in combination with PegINF+RBV). BI 201335 is now in phase III trials in combination with PegINF+RBV and in phase II as part of the interferon-free combination with the polymerase inhibitor, BI 207127, in genotype-1 HCV patients.

Other notable examples are **MK-5172**, a competitive inhibitor of HCV NS3/4A protease that has demonstrated in vitro activity against genotypes 1b, 2a, 2b, and 3a, and proved to be active in vivo against genotypes 1 and 3; and **TMC435** (that can also be administered once-daily), active in therapy-naive patients with HCV G4 infection. Moreover, TMC435 antiviral activity was similar, irrespective of the IL28B genotype. Some compounds, such as **Danoprevir** (formerly R7227/ITMN-191) are being studied in combination with low-dose ritonavir (a pharmacologic booster used for HIV protease inhibitors) in order to improve pharmacokinetics, without increasing toxicity. Whether such complex therapies have the potential to minimize the risk of viral breakthrough and the selection of resistance mutations, remains to be evaluated.

HCV polymerase inhibitors

The HCV NS5B enzyme is an RNA-dependent RNA polymerase essential for viral replication. As the enzyme is highly conserved across all HCV genotypes, the inhibitors are expected to have pan-genotypic activity. The structure of NS5B, like many other viral polymerases (HIV reverse transcriptase included), resembles the shape of a hand consisting of finger, thumb and palm domains. There are two major classes of polymerase inhibitors: nucleoside analogs and non-nucleoside analogs. The enzyme has a catalytic site for nucleoside binding and at least four other sites to which a non-nucleoside molecule could bind and cause allosteric alteration. Inhibitors of NS5B polymerase have advanced to the phase II of clinical development. These agents have demonstrated potent antiviral efficacy, achieving multi-log reductions in HCV RNA with short-term treatment.

Nucleoside analogs target the catalytic sites of the enzyme by competing with natural substrates and, once incorporated, act as chain terminators stopping the further extension of viral RNA nascent strand. This drug class is considered to have the broadest genotypic coverage as well as a high resistance barrier. This is due to the fact that mutations at the active site also affect the viral polymerase fitness.

Several early developed compounds were discontinued because of high toxicity (gastrointestinal or neutropenia related, respectively).

The current most advanced compound in development is the nucleoside analog mericitabine (R7128), an investigational nucleoside inhibitor of NS5B HCV polymerase with antiviral activity against HCV genotypes 1-6. The compound is a prodrug of an oral cytidine nucleoside analog (PSI-6130). A phase IIb trial in therapy-naive patients with genotype 1 or 4 HCV infection demonstrated that a combination of mericitabine and PegIFN/RBV achieves high rates of both rapid and complete early virologic responses. Mericitabine has a safety profile similar to SoC and, importantly, does not seem to be associated with treatment-emergent viral breakthrough or resistance. The combination of this NS5B polymerase inhibitor with an NS3 protease inhibitor (Danoprevir, R7227), administered without additional PegIFN/RBV, for 14 days in treatment-naive, genotype 1-infected patients, demonstrated sustained viral suppression, absence of PI resistant mutations and acceptable safety and tolerability (INFORM 1 trial). The combination is associated with a lower risk of relapse during SoC.

There are several others compounds in early stages of clinical development, that are designed to achieve higher concentrations of the active substance in the liver, reducing systemic exposure and limiting the potential side effects.

The non-nucleoside polymerase inhibitors are a very promising class of molecules, because they target multiple distinct domains on the NS5B polymerase, acting through

allosteric inhibition. HCV polymerase has at least four allosteric binding pockets for nonnucleosidic inhibitors, unlike the HIV reverse transcriptase where there is only a single one. Therefore, if patients do not respond to one non-nucleoside inhibitor, there is enough differentiation between the binding sites to allow the use of a different drug within the class. Several non-nucleoside HCV polymerase inhibitors are in clinical development. Most of these investigational agents are active only against HCV genotypes 1a and 1b and show a relatively high rate of resistance, as well as an increased frequency of specific side-effects. These observations suggest that their use could be limited to combination with other DAAs (Table 4.2). Such an approach was investigated for a low potent non-nucleoside polymerase inhibitor (tegobuvir, formerly known as GS-9190) in combination with a protease inhibitor (GS-9256) in treatment-naive G1 HCV patients. The combination alone, without SoC was not effective due to virologic rebound and selection of dual resistance mutations that existed before treatment. Addition of RBV alone significantly reduced the virologic breakthrough rates.

Table 4.2 – Combinations of DAAs tested with or without PegIFN/RBV

Company	DAA combination	Phase
Vertex	Telaprevir (PI*) + VX-222 (NNI†)	II
Boehringer Ingelheim	BI 201335 (PI) + BI 207127 (NNI)	IIb
Bristol-Myers-Squibb	BMS-650032 (PI) + BMS-790052 (NS5A inhibitor)	II
Gilead	GS-9256 (PI) + GS-9190 (NNI)	II
Hoffmann-La Roche	Danoprevir (R7227) (PI) + R7128 (NI‡)	I

* PI: protease inhibitor

† NNI: non-nucleoside (polymerase) inhibitor

‡ NI: nucleoside (polymerase) inhibitor

NS5A inhibitors

NS5A is a membrane-associated phosphoprotein involved in both the formation of the replication complex and in the virus assembly. The most potent HCV NS5A inhibitor reported to date

is **BMS-790052**, currently in phase II clinical trial in combination with SoC. It was also used in combination with a protease inhibitor (BMS-650032) for retreatment of previous non-responders to SoC with good results, but only in association with PegIFN/RBV. Exclusion of SoC from the therapeutic regimen resulted in high rates of viral breakthrough through week 12.

Host cyclophilins inhibitors

Another interesting therapeutic approach is directed at host factors important in the viral life cycle. The most promising target are cyclophilins, a family of highly conserved cellular peptidyl-prolyl isomerases (PPIase) involved in many cellular processes such as protein folding and trafficking. Cyclophilin inhibitors block the interaction of cyclophilins with HCV proteins and hence the formation of a functional viral replication complex. Currently, several non-immunosuppressive cyclosporin analogs are being tested. The most potent seems to be **Alisporivir (Debio-025)**, tested in both HCV monoinfected and HIV/HCV coinfected patients with promising results. The combination of Debio 025 and PegIFN-α2a showed a significant VL reduction after 28 days in patients infected with genotypes 1, 3 and 4 (Flisiak 2009). Such host protein-targeting compounds have the advantage of higher genetic barriers to resistance and could be instrumental in future IFN-free regimens (Table 4.3).

Emergence of drug resistant mutations

High levels of baseline drug resistance mutations in the NS3 protease or NS5B polymerase were identified in a significant number of viral isolates from treatment-naive patients. Moreover, there seem to be differences between HCV genotypes/subtypes in terms of the frequencies of baseline mutations and natural polymorphisms which can translate into distinct susceptibility to DAAs. An overlap of immune escape and drug resistance profiles has also been reported (Gaudieri 2009).

The majority of DAAs have a low genetic barrier to resistance, with the possible exception of nucleoside analogs inhibitors of HCV polymerase.

There is broad cross resistance between drugs in the same class, as has been shown for the two approved PIs, telaprevir and boceprevir. Possible exceptions are the non-nucleoside inhibitors of HCV polymerase that might be administered in additive or synergistic combinations. The majority of patients with virologic breakthrough during triple therapy with PIs presented high-level resistant variants, these emerged more frequently in the HCV genotype 1a patients (Kuntzen 2008); predominant mutations were V36M and R155K compared to A156T in genotype 1b. There is no information regarding the possible archiving of drug resistant mutants in cellular sanctuaries, as is the case for HIV. Emergence of resistance may be limited by optimized pharmacokinetics of the DAAs and by their use in combinations.

What does the future hold?

In the near future, trials of SoC plus STAT-C will be initiated in difficult-to-treat populations (patients with advanced liver disease, cirrhosis, recipients of liver transplantation or patients with major comorbidities such as HIV coinfection). It remains to be seen if there are safer regimens with less drug interactions, especially with antiretroviral drugs (Seden 2010). As shown in chapter 1, race is an important determinant of the therapy response; as a consequence new HCV therapies should be also studied in Asian, Afro-american and Latino populations in order to fully characterize their efficacy and safety.

The predictive value of on-treatment viral kinetics will require re-evaluation for the DAAs and their combinations. Although evaluation of SVR at 6 months after treatment completion will remain the gold standard for treatment success, there is growing evidence indicating that SVR at 12 weeks after treatment completion may be enough to predict long-term viral clearance.

Preliminary data show that DAAs induce a more rapid decline in the VL than the one seen with PegIFN/RBV.

Table 4.3 – The most promising new therapeutical options for CHC (as of June 2011) *

Category	Mechanism	Example	Manufacturer	Phase
Direct-acting antivirals	NS3/NS4A protease inhibitors	BI201335	Boehringer	III
		TMC435	Medivir/Tibotec	III
		GS-9256, -9451	Gilead	II
		Danoprevir	Intermune/Roche	II
		Vaniprevir	Merck	II
		ACH-1625	Achillon Pharm.	II
		ABT 450	Abbott/Enanta	II
		BMS-650032	Bristol-Myers Squibb	IIa
	NS5B polymerase inhibitors, **nucleoside** analogs	Mericitabine	Roche/Pharmaset	II
		PSI-7977	Pharmaset	II
		IDX 184	Idenix	II
	NS5B polymerase inhibitors, **non-nucleoside** analogs	Filibuvir	Pfizer	II
		GS-9190	Gilead	II
		VX 222	Vertex	II
		ABT 333, -072	Abbott	II
		Setrobuvir	Anadys Pharm.	II
	NS5A inhibitors	BMS-790052	Bristol-Myers Squibb	II
		ABT 267	Abbott	II
		AZD 7295	AstraZeneca	II
Host targeting agents	Cyclophilins inhibitors	Alisporivir	Novartis/Debiopharm	III
	Virus entry inhibitors	MBL-HCV1 human monoclonal antibody	The University of Massachusetts Medical School	II
		ITX 5061	iTherX	II
		Bavituximab	Peregrine Pharm.	II

* For more information, see http://hcvdrugs.com and the manufacturers' web sites presented at the end of the chapter.

Resistance testing is likely to become a part of the treatment algorithm with the introduction of DAAs. Extensive knowledge of the impact of these mutations on the phenotypic characteristics and on the replicative fitness of the viral population will be important (Kuntzen 2008) in order to tailor therapeutic decisions for the management of the HCV infected patient.

It is expected that the HIV model of development of highly active combined therapies, consisting of at least 3 drugs with different mechanisms of action will be reproduced for HCV, in an attempt to obtain effective interferon-free regimens. With such combinations, HCV may become the first chronic viral infection to be cured. While sufficient suppression of HIV RNA and HBV DNA can only be achieved by long-term administration of potent antiviral drugs, HCV RNA may be completely eradicated from the infected individual after a limited duration of treatment. This is foreseeable due to the fact that, unlike HIV (that replicates through a proviral DNA subsequently integrated into the lymphocytes nucleus), or HBV (that replicates through a cccDNA that may integrate into the hepatocyte nucleus), HCV replication is entirely intra-cytoplasmic and is not accompanied by the establishment of extrahepatic reservoirs. In a viral kinetic model for the pharmacokinetics of telaprevir, a rapid decrease in the second slope of viral decline was found, four fold higher than with standard interferon therapy. According to these data, a combination triple therapy administered for 7-10 weeks might be sufficient to eradicate the virus in fully compliant patients (Guejd 2011). Patients who ultimately fail to clear the virus with combination STAT-C regimens may still have improvements in liver histology that can be further sustained by introduction of a separate group of anti-fibrotic agents.

Outlook

The SoC for first-line treatment of HCV genotype 1 will most likely soon become a triple combination of a PI, either boceprevir or telaprevir, with PegIFN/RBV. Individualized treatment must take into account baseline viral, host and disease

characteristics, as well as reviewed on-treatment predictors and detection of resistant mutations. The importance of genetic markers such as the IL28B polymorphism on the SVR during triple therapy is not yet known.

According to the available data, the combinations of DAAs will still require a backbone of PegIFN/RBV in order to attain complete viral suppression and to avoid virologic breakthrough and resistance. However, this will be affected by costs, increased toxicities and emergence of viral resistance. For this reason, a lot of effort is directed to the parallel development of multidrug regimens that may offer independence from PegIFN/RBV, providing new hope for patients who are intolerant or have contraindications to to PegIFN/RBV. Future treatment strategies will include combinations of several DAAs with different mechanisms of action, together with host modulators and drugs addressing innate immunity against HCV.

Links

- European Agency for Medicines: www.ema.europa.eu
- U.S. Food and Drug Administration (FDA): www.fda.gov/Drugs
- EASL: 5th Clinical Practice Guidelines on the Management of Hepatitis C Virus Infection: www.easl.eu/_clinical-practice-guideline
- Treatment for chronic hepatitis C and co-infection with HIV/HCV: www.hivandhepatitis.com
- Hepatitis C Medication: http://pharmexec.findpharma.com

- Abbott: www.abbott.com
- Achillion Pharmaceuticals: www.achillion.com
- Anadys Pharmaceuticals: www.anadyspharma.com
- AstraZeneca : www.astrazeneca.com
- BMS: www.bms.com
- Boehringer Ingelheim: www.boehringer-ingelheim.com
- Gilead: www.gilead.com
- IDX: www.idenix.com

- iTherX: www.itherx.com
- Merk: www.merck.com
- Novartis: www.novartis.com
- Peregrine Pharmaceuticals: www.peregrineinc.com
- Pharmasset: www.pharmasset.com
- Pfizer: www.pfizer.com
- Roche: www.roche.com
- Tibotec: www.tibotec.com
- Vertex: www.vrtx.com

5. Management of recurrent HCV infection following liver transplantation

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Natural history of recurrent HCV infection after liver transplantation

Chronic hepatitis C (CHC) is a worldwide health problem and, despite a decline in the incidence of new HCV infections, the prevalence of cirrhosis and the incidence of its complications will not peak until the year 2040 (Davis 2003). CHC has become the leading indication for both cadaveric and living donor liver transplantation (LT), accounting for approximately 50% of cases in the United States, Europe and Japan.

Demand does not slow down because of the constant increase of the number of patients with HCV end-stage liver disease (ESLD) and HCH.

Unfortunately, HCV infection invariably recurs after LT and the natural course of the disease is accelerated compared to the non-transplant setting. The influence of HCV infection on allograft histology is highly variable, but at least 50% of recipients develop histological evidence of recurrent disease within 1 year

post-transplant. The progression of fibrosis occurs at a rate 1.4 times faster when compared to progression of fibrosis in the non-transplant population (Mohsen 2003).

The estimated rate of allograft cirrhosis reaches 30% at 5 years of follow-up, leading to increasing incidence of retransplantation in HCV recipients. After the diagnosis of cirrhosis, the decompensation risk appears to be accelerated (17% and 42% at 6 and 12 months, respectively). Patient survival is also significantly decreased: 66% and 30% at 1 and 5 years, respectively (Berenguer 2000). HCV infection-associated allograft injury is incriminated as the most common cause of both death (28-39%) and graft failure (~40%) among transplant recipients (Charlton 2004). Retransplantation represents the last option for these patients in the context of increasing demands for LT.

Many factors such as donor and host characteristics, virologic features and immunosuppression have been shown to influence the progression of post-transplant liver disease.

Viral factors. As early as the first week postoperatively, the HCV RNA level increases 10- to 20-fold and plateaus at 1 month, with higher levels noted in those with more severe recurrent hepatitis (Berenguer 2001). However, the role of HCV RNA levels in determining severity of HCV recurrence remains controversial. The single exception is the well-proven relationship between very high VL and occurrence of cholestatic hepatitis (~2-5% of patients). Other viral factors that may influence the severity of the recurrence are difficult-to-treat viral genotype (1 and 4) and the quasi-species.

Recipient factors. Increasing age of the recipient (>50 years) and female sex, as well as non-Caucasian (Afro-American, Asian) have a more aggressive recurrence (Belli 2007). Thus, a combination of a liver from an old donor with an old recipient should be avoided. Presence of a necroinflammatory score ≥2 in the explants was shown to be a predictor of progressive fibrosis. Also, the HLA donor-recipient matching was associated with a

more severe HCV recurrence, although overall graft survival was not influenced (Langrehr 2006).

Donor factors. Evidence suggests the following donor factors to be associated with negative outcome in HCV-infected LT recipients: donor age, donor fat content (>30%) and ischemic time. Older donor age (≥50 years) was an independent predictor for HCV related cirrhosis after 5 years and reduced graft survival in several studies (Iacob 2007, Samonakis 2005). Prolonged warm ischemia time (begins as the liver is secured in place and extends until reperfusion with recipient blood starts) represents a higher risk for a severe histological recurrence; this risk increases by 13% for each hour increase of cold ischemia time (time elapsed between removal and cooling of the donor liver and extends until the donor liver is rewarmed during implantation). Recent studies have demonstrated that living-related LT is not a risk factor for severe HCV recurrence. The HCV histological recurrence rate was 58% after 4 months, 90% at 1 year and 100% after 2 years in patients transplanted with a living donor compared to 71% at 4 months, 94% at 1 year and 95%, respectively, after 2 years in deceased donor LT (Guo 2006).

Clinical factors. A number of potentially modifiable post-transplant factors have also been associated with increased severity of HCV recurrence and poorer patient and graft survival such as immunosuppression, acute rejection episodes treated with bolus corticosteroids or T-lymphocyte depleting agents, cytomegalovirus or herpes simplex 6 virus infection, metabolic syndrome or insulin resistance.

Much emphasis has been placed on the different **immunosuppressive regimens** and their changes during the last 20 years. CHC is more aggressive in LT recipients than in immuno-competent patients. However, a sudden change in the degree of immunosuppression, rather than the absolute amount of immunosuppression, is deleterious for HCV-infected recipients.

Regarding the calcineurin inhibitors (CNI), most of the studies suggest that there is no significant difference between

tacrolimus and cyclosporine with respect to their impact on histologically diagnosed HCV recurrence and graft or patient survival (Iacob 2007, Berenguer 2007). Cyclosporine has a strong in vitro suppressive effect on HCV replication (Watashi 2003). Several clinical although relatively small studies suggested a higher sustained virologic response (SVR) in HCV LT patients receiving cyclosporine and interferon therapy.

The cornerstone of immunosuppressive agents, the corticosteroids, slowly tapered off over a long time, may prevent progression to severe forms of recurrent disease (Iacob 2007, Brillanti 2002). In contrast, the boluses of methylprednisolone (MP) used for acute rejection episodes were deleterious to the HCV-related graft survival. Outcome of HCV-positive patients who received multiple pulses of MP is significantly worse than that in patients with a single pulse therapy (Bahra 2005). High levels of viremia can determine an HCV-cytopathic mechanism involved in the allograft injury. Currently, steroid-free immunosuppression regimens are preferred in HCV recipients.

Actual data for mycophenolate mofetil (MMF), a morpholino ester prodrug of mycophenolic acid (MPA), favor its use in recurrent hepatitis C. MPA is a selective, noncompetitive, reversible inhibitor of inosine monophosphate dehydrogenase (IMPD), a key enzyme in the biosynthetic pathway of the guanine nucleotides. It is also a potent inhibitor of both B and T cell proliferation. MMF in combination with CNI taper showed a positive effect on fibrosis progression, graft inflammation and ALT levels (Lake 2009, Iacob 2007). Less data are available for azathioprine, but its inclusion in the maintenance regimen was associated with survival advantage.

The potential antifibrotic and antiviral benefit of mTOR (mammalian target of rapamycin) inhibitors after LT in HCV positive patients awaits further investigation in prospective randomized controlled trials. Sirolimus, a macrolide isolated from *Streptomyces hygroscopius* reduces TGF-β and procollagen, inhibits hepatic stellate cell proliferation and may have an inhibitory action on HCV replication through phosphorylation of

signal transducers and activators of transcription (STAT-1) (Matsumoto 2009).

Prophylactic antiviral therapy in cirrhosis

The main goals of treating cirrhotic patients with antiviral therapy are to prevent the complications of the disease, to halt disease progression or allow for the regression of cirrhosis, and to attain sustained viral clearance in order to prevent reinfection in the graft in patients undergoing LT.

SVR in patients with Child-Pugh (CP) class A cirrhosis has improved from 5% with interferon monotherapy to 50% with pegylated interferon alfa (PegIFN) + ribavirin (RBV) in genotype 1 (Everson 2005).

The safety of combination therapy in cirrhotics is a major concern. Bone marrow suppression by administration of either standard or PegIFN alfa leads to significant decrease in all three lineages of the hematopoietic system (Iacobellis 2008). However, erythropoietic agents are effective in treating anemia, preventing RBV dose reduction, improving patients' quality of life, but the effect on SVR is not fully elucidated. Granulocyte colony-stimulating factor is effective in raising ANC; however, neutropenic HCV-infected patients on combination treatment may not experience increased bacterial infections. Eltrombopag, a new oral thrombopoietin mimetic, may allow combination treatment in patients with cirrhosis and thrombocytopenia.

Antiviral therapy is commonly deferred in cirrhotics with signs of liver decompensation, due to even more compelling concerns over treatment-induced side effects (up to 60%).

There are several studies reporting experience with interferon-based therapy in pre-transplant patients aiming to prevent reinfection of the new graft (Alsatie 2007). The largest study (Everson 2005) included 124 patients with an average CP score of 7.4 and a mean MELD (Model for End Stage Liver Disease – the currently used allocation system, introduced in 2002 in USA in order to prioritize patients on the waiting list) score of 11, who received a low-accelerating-dose regimen. An SVR of 24% was

achieved and 12 of 15 patients who were HCV RNA-negative before LT remained HCV RNA-negative ≥6 months postoperatively. The following predictors of response in these studies were identified: non-1 genotype, CTP class A (genotype 1 only), ability to tolerate full dose and duration of treatment, lower pretreatment VL, a VL decrease ≥2 $\log_{10}$ at week 4 of treatment (Alsatie 2007). Premature discontinuation of the therapy due to side effects was reported in 13-30% and dose reductions were more frequent.

On the basis of available data, prophylactic antiviral therapy in this setting to prevent recurrent HCV infection post-LT has a limited role and may be associated with serious AEs. Pretransplant therapy, using a low-accelerating dose regimen, is an important treatment strategy but is applicable to selected patients only. Prophylactic antiviral therapy should not be considered in those with high MELD score (≥20) or CTP class B or C. It is to be noted that up to two-thirds of patients who become HCV RNA–negative on treatment will be HCV-free post-transplantation.

Pre-emptive antiviral therapy after LT

Preemptive antiviral therapy started within 2-6 weeks after transplantation has the advantage of a relatively low VL and the absence or minimal evidence of histologic recurrence, but is limited by tolerability, particularly in patients with high MELD scores pre-transplantation.

Rates of SVR vary from 5% to 39% (Terrault 2008). Better results were reported in adult-to-adult right lobe live donor LT for HCC and low MELD scores as well as in planned living donor LT cases with splenectomy (Sugawara 2010). Dose reductions were required, more frequently for RBV than interferon, and treatment discontinuations were highly variable across the studies, ranging from 0% to 57%.

Two small trials have evaluated the efficacy of PegIFN in this setting, one of which noted that only 41% of screened transplant recipients were eligible to begin therapy (Chalasani 2005).

Histological benefits in virologic nonresponders have been demonstrated in a study where only 22% in a group receiving preemptive therapy progressed vs. 49% of patients not receiving preemptive therapy (Kuo 2008). However, this prophylactic approach cannot be used in a considerable proportion of patients due to initially intense immunosuppression, pancytopenia, postoperative infections and insufficient recovery after the surgery.

Therapy of recurrent hepatitis C after LT

Posttransplant antiviral therapy in recipients with evidence of biochemical and histological recurrent disease, usually 6 months after LT, is the mainstay of management. Although a high number of transplant centers use antiviral therapy, the treatment is not standardized and is still associated with low rates of SVR, less than those reported in the non-transplant setting. The main reasons include high VL post-LT, a higher frequency of genotype 1 patients, poor tolerability of treatment after LT, and need for frequent dose reductions.

The combination of PegIFN/RBV is the treatment of choice also in transplant recipients. The SVR associated with PegIFN/RBV therapy in predominantly genotype 1 infected populations has been reported to range from 12% to as high as 50% (Gonzalez 2010). A recent extensive review of 19 prospective and retrospective clinical studies describing antiviral therapy with PegIFN/RBV in this population reported a mean SVR of 30.2% (Berenguer 2008). End of treatment virologic response (EoTR) was 42.2% (range 17-68%), indicating that relapse was a major factor in the low SVR rates. Biochemical responses were registered in 54.8% and histological endpoints were judged to be too heterogeneous in definition and assessment to provide a summary estimate. However, it was noted that histological improvements were generally confined to treated patients who achieve SVR. Fibrosis has been shown to progress significantly more in nonresponders to antiviral therapy. Even in the absence of virological response, the rate of progression of fibrosis was

significantly slowed in patients treated for more than 6 months (Walter 2009). Using long-term maintenance antiviral therapy has recently been shown to increase the probability of biochemical and histological responses, regardless of the timing of the HCV recurrence (de Martin 2010).

Achievement of SVR in the setting of recurrent HCV following LT has a major impact on long-term outcomes, including improved graft and patient survival. Identifying patients with a greater likelihood of achieving SVR is an important consideration in the selection of potential treatment candidates and is a key factor in developing strategies for optimizing response to therapy.

Predictors of response to therapy identified in different studies (Terrault 2008, Selzner 2009, Gonzalez 2010, Fukuhara 2010) were

- Non-1 HCV genotype
- Absence of prior antiviral therapy
- Donor age
- Pretreatment necroinflammatory activity and fibrosis stage
- Concomitant cyclosporine use
- Course completion (the rule of 80/80/80, see chapter 1)
- Low pretreatment HCV RNA (<1 million IU/ml)
- IL28B polymorphism in recipient and donor tissues
- RVR or EVR – that hold the highest predictive values of SVR. Undetectable VL at 24 weeks of therapy was also noted to confer a high predictive value (92%) for SVR and prolonged treatment protocol was suggested in these LT recipients.

Side effects and safety of PegIFN/RBV therapy

The clinical spectrum of AEs is similar to the non-transplant setting (see chapter 1). Dose reductions are frequent and drug discontinuation rates are higher than in nontransplant patients.

A major limitation of antiviral therapy is tolerability, particularly with respect to the hematologic AEs of PegIFN/RBV. In a recent Cochrane review, up to 87.5% of patients required a dose reduction and up to 42.9% of patients stopped treatment

because of AEs or because of patient's choice to stop it (Gurusamy 2010). Cytopenias, mood disturbances, and acute cellular rejection are the most common reasons for dose reduction or discontinuation (Terrault 2008). The use of growth factors is required to manage cytopenias (anemia and neutropenia) in up to 50% of patients, and thus to improve tolerability. However, there is not enough evidence to support improvement of SVR with concomitant use of Filgastrim and/or erythropoietin. Anemia is a common side effect especially in older LT recipients and with a low BMI (Saab 2007). RBV toxicity can be of concern in LT recipients with renal dysfunction. Lower initial RBV dosing, increasing as tolerated, or dosing based on a nomogram that incorporates renal function (creatinine clearance) is highly recommended (Watt 2009).

Acute cellular rejection (ACR) and chronic ductopenic rejection are immune-mediated complications unique to the post-transplant setting. Acute and chronic rejections are infrequent complications of antiviral therapy often associated with concomitant low or negative serum HCV RNA. The reported incidence of ACR during interferon based therapy ranges from 0 to 35%. It is to be noted that the incidence of ACR in HCV positive LT recipients treated with combination antiviral therapy for HCV recurrence does not seem to be higher than that observed in non treated HCV positive LT recipients (Seltzner 2010).

An autoimmune-like hepatitis (de novo autoimmune hepatitis) has been reported in LT recipients treated with PegIFN/RBV for recurrent hepatitis C. In general, these patients have no history of autoimmune disease, and HCV RNA is undetectable at the time of the secondary rise in liver enzymes. In HCV infected patients, it remains controversial whether these cases represent a true autoimmune (alloimmune) process, as opposed to an atypical manifestation of recurrent disease or of acute or chronic allograft rejection. Histologic findings are an essential part in the differential diagnosis between these entities. Any flare in liver enzymes in patients treated with antiviral therapy, particularly in those with undetectable HCV RNA, should raise

the suspicion of these complications and warrant the performance of a liver biopsy.

Retransplantation for recurrent HCV cirrhosis

Retransplantation is the only therapeutic option to achieve long-term survival in patients with decompensated HCV cirrhosis after LT. Retransplantation for this indication ranges from 3.6% to 44%. Patient and graft survival rates after retransplantation are inferior to those after primary LT. HCV-infected recipients had a significantly lower survival rate compared to non-HCV-infected patients who underwent retransplantation at least 90 days after primary LT.

Progression to cirrhosis is faster after retransplantation than after primary LT, particularly in patients with severe hepatitis C recurrence (cholestatic hepatitis and graft failure within the first year) (Carrion 2010). Predictors of poor outcome are: bilirubin ≥10 mg/dL, serum creatinine ≥2 mg/dL, donor age >40, recipient age >55 and early HCV recurrence (cirrhosis <1 year after LT) (Wiesner 2003). Thus, the optimal timing to perform elective retransplantation in HCV patients is a matter of debate. However, bilirubin and creatinine serum levels are essential for deciding about retransplantation candidates. Patients with a CTP score ≥10 or a MELD score >25 have a very high risk of death after retransplantation.

Outlook

HCV is and will continue to be the most common indication for LT worldwide and recurrent disease associated with HCV is a major cause of allograft loss and mortality.

A better understanding of the recipient, donor and viral risk factors for progressive disease and vigilant post-transplant monitoring through histologic assessment may guide management aimed toward reducing the potential for graft failure as well as helping identify candidates for antiviral therapy.

Antiviral therapy in patients with HCV cirrhosis awaiting LT should be considered only in selected individuals due to poor tolerability and limited virologic response. Pre-emptive therapy is not well tolerated in the post-LT population. Antiviral therapy with PegIFN/RBV should be considered in transplant recipients with recurrent HCV infection. Achievement of SVR is associated with increased allograft and patient survival; however, efficacy may be limited by poor tolerability, risk of cellular rejection and risk of alloimmune hepatitis, requirement for dose reductions, and treatment discontinuation.

Retransplantation is the only therapeutic option to achieve long-term survival in patients with decompensated cirrhosis after LT.

Links

- American Liver Foundation: www.liverfoundation.org
- The United Network for organ sharing (UNOS): www.unos.org
- American College of Gastroenterology, Hepatitis C Treatment Resource Kit (PDF, 56 pages): goo.gl/qCz3v
- European Liver Transplant Registry: www.eltr.org
- Organ Procurement and Transplantation Network (OPTN): http://optn.transplant.hrsa.gov

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7. Appendix – Selected drug profiles

Simona Ruta and Costin Cernescu

The following highlights do not include all the information needed to use the drugs safely and effectively. See full prescribing information for each drug.

Pegasys™

(pegylated interferon alfa-2a 40 kD)
Drug class: Cytokine, interferon.
Manufacturer: Hoffmann-La Roche, Inc.
Indications: Chronic hepatitis C, possibly also for hepatitis B. Pegasys, alone or in combination with ribavirin (Copegus), is indicated for the treatment of adults with CHC who have compensated liver disease and have not been previously treated with IFN alfa. Efficacy has also been demonstrated in subjects with histological evidence of cirrhosis (Child Pugh class A) and in subjects with clinically stable HIV disease and CD4 count >100 cells/mm2.
Pegasys is also indicated for the treatment of adult patients with HbeAg-positive and HbeAg-negative chronic hepatitis B who have compensated liver disease and evidence of viral replication and liver inflammation.
Dose: 180 µg, once per week.

Combination therapy with ribavirin (Copegus™) with different posology according to HCV genotypes.
Side effects: Influenza-like symptoms (fever, myalgia), neuropsychiatric events (depression, fatigue, sleeping disorders, personality changes), bone marrow toxicity (anemia, thrombocytopenia, leucopenia), endocrine disorders, cardiovascular events, pulmonary disorders, gastrointestinal events, development or exacerbation of autoimmune and ophthalmologic disorders, hypersensitivity reactions, hair loss. **All side effects are usually reversible.** Patients with persistently severe or worsening signs or symptoms should be withdrawn from therapy.
Contraindications: Severe heart or liver or renal dysfunction, bone marrow disorders, CNS disorders (epilepsy, severe depression), uncompensated thyroid disorders, autoimmune hepatitis, hypersensitivity reactions.

Reference

Ferenci P, Fried MW, Shiffman ML, et al. Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2a (40KD)/ribavirin. J Hepatol 2005;43:425-33.

Internet links

Hoffmann-La Roche: www.roche.com
PEGASYS: www.pegasys.com
FDA, Medication Guide (PDF, 18 pages): goo.gl/vRvqi

PegIntron™

(pegylated interferon alfa-2b, 12 kd)
Drug class: Cytokine, interferon.
Manufacturer: Schering Corporation/Merck.
Indications: Treatment of chronic hepatitis C in patients 3 years of age and older with compensated liver disease who have not been previously treated with IFN alfa.

Dose: 1.5 µg/kg once per week, administered by subcutaneous injection. For pediatric use, the recommended dose, based on body surface area, is 60 mcg/m^2/week.
Combination: PegIntron (1.5 mcg/kg/week) with ribavirin (Rebetol™) 800-1400 mg/day or 15 mg/kg/day. Duration is dependent on HCV genotype. Dose reduction is recommended in patients experiencing adverse events or renal dysfunction.
Side effects and contraindications: Similar with Pegasys.

Reference

McHutchison J, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009;361:580–93.

Internet links

PegIntron: www.pegintron.com
FDA, Medication Guide (PDF, 14 pages): goo.gl/30CcP
Merck: www.merck.com

Infergen™

Class: Cytokine, interferon, interferon alfacon.
Manufacturer: Boehringer Ingelheim Pharma GmbH & Co. Biberach, Germany for: Three Rivers Pharmaceuticals, LLC.
Indications: Infergen in combination with ribavirin is administred for HCV-infected patients who failed to respond to previous treatment with PegIFN/RBV. Patients with the following characteristics are less likely to benefit from treatment with interferon alfacon-1 and ribavirin: response of <1 $\log_{10}$ drop HCV RNA on previous treatment, genotype 1, high VL (>850,000 IU/mL), African-American origin, and/or presence of cirrhosis.
Dose (Combination treatment): Infergen 15 mcg daily with ribavirin 1,000 or 1,200 mg (for body weight < 75 kg and ≥ 75 kg) daily for up to 48 weeks (as retreatment). Dose reduction is recommended in patients experiencing serious adverse reactions.

Side effects: fatigue, fever, rigors, body pain, headache, abdominal pain, nausea, granulocytopenia, arthralgia, myalgia, back pain, neutropenia, and influenza-like illness.

Reference

Ho SB, Aqel B, Dieperink E, et al. U.S. multicenter pilot study of daily consensus interferon (CIFN) plus ribavirin for "difficult-to-treat" HCV genotype 1 patients. Dig Dis Sci 2011;56:880-8.

Internet links

Infergen: www.infergen.com
FDA, Prescribing Information (PDF, 39 pages): goo.gl/kvChY
Three Rivers Pharmaceuticals:
http://www.3riverspharma.com/products.htm

Ribavirin

Manufacturers: Roche (Copegus™, 200 mg film-coated tablets), Merck/Schering-Plough (Rebetol™, 200 mg hard capsules or solution: 40 mg/ml).
Generics Trade Names: RibaPak™, Ribasphere™, RibaTab™, Ribavirin, Virazole™, Virazid™, Viramid™.
Drug class: Virostatic.
Indication: Ribavirin is a nucleoside analog indicated in combination with IFN alfa-2a and 2b (pegylated and non-pegylated) for the treatment of chronic hepatitis C infection in patients 3 years of age or older with compensated liver disease. RBV monotherapy is not effective for the treatment of CHC.
Dose: 800-1200 mg administered daily, orally in two divided doses. The dose should be individualized, depending on body weight and baseline disease characteristics, response to therapy and tolerability of the regimen.
Side effects: The most important side effect is reversible hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to myocardial infarctions. Dose reduction (600-800 mg/day) may be necessary in cases of severe anemia (hemoglobin <10 g/dl). However, always consider erythropoietin before dose reduction,

as there is a linear correlation between mg/kg ribavirin dose and treatment success. Discontinuation of ribavirin may be necessary at hemoglobin values < 8.5 g/dl.
Contraindications: Pregnancy, severe coronary disease, renal failure, decompensated liver cirrhosis, hemoglobinopathies (e.g., thalassemia major or sickle-cell anemia).
Warning: Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to Ribavirin. Therefore, its use is contraindicated in women who are pregnant and in the male partners of women who are pregnant. At least two reliable forms of effective contraception must be utilized during treatment and during the 6 month post-treatment follow-up period.

References

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Pawlotsky JM, Dahari H, Neumann AU, et al. Antiviral action of ribavirin in chronic hepatitis C. Gastroenterology 2004;126:703-14.

Bronowicki JP, Ouzan D, Asselah T, et al. Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa-2a plus ribavirin. Gastroenterology 2006;131:1040-8.

Internet sources

Hoffmann La Roche: www.roche.com
Merk: www.merck.com
Official FDA information for ribavirin:
www.drugs.com/pro/ribavirin.html

Incivek™ (Telaprevir)

Manufacturer: Vertex Pharmaceuticals Incorporated.
Indications: Telaprevir is a HCV NS3/4A protease inhibitor indicated for the treatment of genotype 1 chronic hepatitis C infection, in combination with PegIFN/RBV, in adult patients with compensated liver disease, including cirrhosis, who are treatment-naive or who have been previously treated with IFN-based treatment, including prior null responders, partial

responders, and relapsers. Telaprevir must not be used as monotherapy.
Presentation: 375 mg film-coated tablet, oral administration.
Dosage and administration: 750 mg taken 3 times a day (7-9 hours apart) with food. Telaprevir **must be administered with both PegIFN alfa and RBV** for all patients for 12 weeks, followed by a response-guided regimen of either 12 or 36 additional weeks of PegIFN/RBV, depending on viral response and prior response status.
Side effects: Rash, pruritus, anemia, nausea, hemorrhoids, diarrhea, anorectal discomfort, dysgeusia, fatigue, vomiting. Serious skin reactions, including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) and Stevens-Johnson syndrome were reported in less than 1% of subjects. If a serious skin reaction occurs, all components of telaprevir combination treatment must be discontinued immediately. The addition of telaprevir to PegIFN/RBV is associated with an additional decrease in hemoglobin concentrations. All contraindications to PegIFN alfa and RBV also apply, since telaprevir must be administered only in triple therapy.

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Zeuzem S , Andreone P, Pol S, Lawitz E, et al. Telaprevir for retreatment of HCV infection. N Engl J Med 2011;364:2417-28.

Internet sources

Incivek: www.incivek.com
FDA, Prescribing Information (PDF, 23 pages): goo.gl/k2VMV
Vertex Pharmaceuticals: www.vrtx.com

Victrelis™ (Boceprevir)

Manufacturer: Schering Corporation/Merck & co., Inc.
Indications: Boceprevir is a NS3/4A protease inhibitor indicated for the treatment of CHC genotype 1 infection, in combination with PegIFN/RBV, in adult patients (≥18 years of age) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous IFN and RBV therapy. Boceprevir in combination with PegIFN/RBV has not been studied in patients documented to be historical null responders (less than a 2 $\log_{10}$ HCV RNA decline by treatment week 12) during prior therapy with PegIFN/RBV. Boceprevir must not be used as a monotherapy.
Presentation: Capsules 200 mg.
Dosage: 800 mg three times daily (every 7-9 hours). Therapy is initiated with PegIFN/RBV for 4 weeks. Boceprevir is added to PegIFN/RBV regimen after 4 weeks of treatment. Based on the patient's HCV RNA levels at treatment weeks 8, 12 and 24, response-guided therapy may be used to determine duration of treatment.
Side effects: The most commonly reported adverse reactions (greater than 35% of subjects) in clinical trials were fatigue, anemia (the addition of Boceprevir to PegIFN/RBV is associated with an additional decrease in hemoglobin concentrations), nausea, headache and dysgeusia (alteration of taste). All contraindications to PegIFN alfa and RBV also apply since Boceprevir must be administered only in triple therapy.

References

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Internet sources

Victrelis: www.victrelis.com
FDA, Prescribing Information (PDF, 26 pages): goo.gl/eFwuJ
Merk: www.merck.com

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#4

Chronic hepatitis C is associated with substantial morbidity. Although effective treatment is now available, less than half of the infections are diagnosed, relatively few are referred for treatment, and misperceptions abound among patients and physicians alike.

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ISBN 978-3-942687-04-1