Diploma Thesis

Quantification of infectious adverse events associated with dual- and triple-therapy in patients suffering from Hepatitis C

at the Division of Gastroenterology and Hepatology, between June 2009 and April 2014. A retrospective study including 108 patients

submitted by

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Declaration

I hereby declare that this thesis is my original work and it has been written by me in its entirety. I have acknowledged all the sources of information which have been used in the thesis.

Graz, June 3, 2014 *Martin Horn*

Acknowledgement

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Zusammenfassung

Die Anzahl der chronisch mit dem Hepatitis C Virus infizierten Patienten wird weltweit auf 130 – 210 Millionen, entsprechend ca. 3% der Weltbevölkerung geschätzt. Insgesamt zählen Hepatitis-C-Infektionen zu den häufigsten Ursachen chronischer Lebererkrankungen weltweit.

Die gegenwärtige Standardtherapie für Patienten mit chronischer Hepatitis C basiert auf einer Kombination aus Peginterferon und Ribavirin (Dualtherapie), seit wenigen Jahren optional zusätzlich mit einem oralen Proteaseinhibitor (Tripletherapie).Das Auftreten von Nebenwirkungen sowie deren Schweregrad hängt im Allgemeinen vom verwendeten Therapieregime und im Speziellen von Medikamentendosis, Häufigkeit der Einnahme bzw. Verabreichung, sowie dem Applikationsweg ab.

Zu den häufigen Nebenwirkungen (betrifft bis zu 95% der Patienten) gehören u.a. Fieber, Müdigkeit, Kopfschmerz, Übelkeit, Arthralgien, Depressionen, Hautveränderungen, Neutropenie und Anämie. Im Vergleich der beiden Therapieregime hat sich ein gehäuftes Auftreten von Nebenwirkungen bei der Tripletherapie gezeigt. Insbesondere kommt es zu einem vermehrten Auftreten von Anämie, Neutropenie, Gastrointestinale Symptome, Müdigkeit, Geschmacksstörungen und Hauterscheinungen.

Es wurden vermehrt infektiöse Nebenwirkungen unter Tripletherapie beobachtet, welche unter der Dualtherapie mit Peginterferon und Ribavirin nicht oder nur sehr selten beobachtet werden. Die klinische Bedeutung von Nebenwirkungen der Therapie ist eine Reduktion der Lebensqualität der Patienten und ein damit einhergehender Verlust der Adherenz zur antiviralen Therapie.

Die Früherkennung und die unmittelbare Therapie der Nebenwirkungen sind somit unter Anderem entscheidende Parameter im Heilungserfolg der antiviralen Therapie.

Kernaufgabe der Diplomarbeit ist, das Ausmaß an aufgetretenen (insbesondere infektiösen) Nebenwirkungen unter Dual- bzw. Tripletherapie, von Patienten welche an der klinischen Abteilung für Gastroenterologie und Hepatologie der Medizinischen Universität Graz, im Zeitraum von Juni 2009 bis April 2014 behandelt werden, zu quantifizieren. Dabei ist mit einem gehäuften Auftreten von Nebenwirkungen unter Tripletherapie zu rechnen.

Der theoretische Teil der Diplomarbeit befasst sich mit der Erhebung der aktuellen internationalen Therapieempfehlungen, und der Analyse von möglichen Prädiktorparametern für das Auftreten von Nebenwirkungen unter Therapie sowie dem Therapieerfolg. Da chronische Hepatitis C beide Geschlechter betrifft, ist die angestrebte Zielsetzung für Frauen und Männer gleichermaßen bedeutsam.

Abstract

Hepatitis C Virus infection is one of the main causes of chronic liver disease worldwide with current estimates of approximately 130 – 210 million individuals (according to 3% of the world population) chronically infected with the hepatitis C virus. However, hepatitis C virus infections are among the most common causes leading to chronic hepatitis, liver cirrhosis and liver related death worldwide.

The current standard of care is a combination of pegylated Interferon and Ribavirin (dual-therapy). Since 2011, direct-acting antiviral drugs inhibiting viral protease are approved as an addition to the standard therapy (triple-therapy).

The occurrence of adverse events as well as their severity generally depends on the therapy regimen and is influenced by type and dosage of medications.

Most common adverse events (affects up to 95% of patients) are fever, fatigue, cephalea, nausea, arthralgia, depression, skin reactions, neutropenia, and anemia.

A more frequent occurrence of adverse events with triple-therapy compared to dual-therapy has become clear since it's introduction, particularly with regard to anemia, neutropenia, gastrointestinal discomfort, fatigue, dysgeusia, and skin reactions. However, there is accumulating evidence for a more often appearance of infections and/or infestations in patients receiving triple-therapy.

The medical consequence from adverse events is a reduction of quality of life and consecutively the loss of antiviral therapy adherence. Thus, early recognition and immediate treatment of adverse events are crucial aspects in the success of antiviral treatment.

Aim of this thesis is to quantify reported adverse events with respect to therapy regimen (dual-therapy vs. triple-therapy) in patients who are treated at the Department of Internal Medicine, Division of Gastroenterology and Hepatology at the Medical University Graz. Furthermore, a detailed review of international treatment recommendations, as well as an analysis of possible predictor parameters for the appearance of adverse events and treatment success is done.

This thesis is meaningful for both genders since chronic hepatitis C equally affects female and male subjects.

Contents

Glossary and Abbreviations

BT *Breakthrough*. Virological breakthrough is given if HCV-RNA reappear at any time during treatment after a negative result or increase of $1\log_{10}$ IU/ml from nadir.

BOC *Boceprevir*. First generation protease inhibitor: the antiviral effect of Boceprevir is mediated by binding to HCV nonstructural 3 NS3 (HCV) active site. Indicated only for use against hepatitis C genotype 1 viral infection.

DAA *Direct-acting Antiviral Agents*. These drugs selectively target a virus, in case of Boceprevir and Telaprevir selectively inhibit hepatitis c virus protease.

DVR *Delayed Virological Response*. More than -$2\log_{10}$ IU/ml decrease from baseline but detectable HCV-RNA at week 12 of dual therapy, then undetectable at week 24 and maintained up to end of treatment.

EOT *End Of Treatment*. End of treatment is achieved by patients fulfilling their distinct treatment duration.

eRVR *Extended Rapid Virological Response*. Undetectable HCV-RNA in a sensitive assay at week 4 and 12.

ER *Early response*. Undetectable HCV-RNA in a sensitive assay at week 8 of Boceprevir based triple therapy (after 4 wk of BOC).

EVR *Early Virological Response*. HCV-RNA detectable at week 4 of dual therapy but undetectable at week 12, maintained up to end of treatment.

HAV *Hepatitis A Virus*. HAV is a non-enveloped, single-stranded RNA virus of the family picornavirus, packaged in a protein shell. HAV-infection is a known co-factor in HCV-antiviral therapy.

HBV *Hepatitis B Virus*. HBV is a 42 nm in size, enveloped DNA virus of the family hepadnaviridae. HBV-infection is a known co-factor in HCV-antiviral therapy.

HCV *Hepatitis C Virus*. HCV is a 55 – 65 nm in size, enveloped, positive-sense single-stranded RNA virus of the family Flaviviridae. Hepatitis C virus is the cause of hepatitis C in humans.

HIV *Human Immunodeficiancy Virus*. In HIV-HCV co-infected patients, the Hepatitis C viral load is higher than in HCV-mono-infected patients in both the plasma and liver tissue. Thus making HIV a relevant co-morbidity in HCV antiviral therapy.

IFN *Interferon*. Interferones are proteins made and released by host cells in response to the presence of pathogens such as viruses.

LR *Late response*. Detectable HCV-RNA in a sensitive assay at week 8 of Boceprevir based triple therapy, but negative at week 12 (after 8 weeks of Boceprevir).

NR *Null response*. Less than $2\log_{10}$ IU/ml decrease in HCV-RNA level from baseline at week 12.

PR *Partial response*. More than $2\log_{10}$ IU/ml decrease in HCV-RNA level from baseline at week 12 of antiviraltherapy but HCV-RNA detectable at week 24.

RBV *Ribavirin*. Antiviral effect by interfering viral RNA synthesis and viral mRNA capping. Indicated in combination with interferone in antiviral therapy with all HCV-genotypes. . Patients who have undetectable HCV-RNA at the end of treatment, but do not achieve an SVR due to recurrence of the virus after stoppig treatment.

RNA *Ribonucleic acid*. RNA is a ubiquitous family of large biological molecules that perform multiple vital roles in the coding, decoding, regulation, and expression of genes.

RVR *Rapid virological response*. Undetectable HCV-RNA in a sensitive assay at week 4.

SVR *Sustained Virological Response*. Undetectable HCV-RNA at week 12 (SVR-12), week 24 (SVR-24), and week 48 (SVR-48) of follow up. If no specific time is given (e.g. SVR) it is usually referred to SVR-24.

TVR *Telaprevir*. First generation protease inhibitor: antiviral effect by inhibiting the hepatitis C viral enzyme NS3/4A serine protease. Indicated only for use against hepatitis C genotype 1 viral infection.

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1 Introduction

A brief summary of current treatment guidelines:

This chapter begins with **General Considerations** (➪ page 2) about the infection with the hepatitis C virus and necessary information for treatment decisions.

Subsequently **Screening and Treatment Selection** (➪ page 5) deals with the pre-treatment screening and the decision whether or not an antiviral therapy should be initiated and which therapy regime should be used.

The aim of **Treatment** (➪ page 14) a brief discussion of goals and endpoints of chronic hepatitis C therapy, dosage of antiviral medication, treatment process and duration and follow up after end of treatment is given.

Finally **Clinical Presentation** and Adverse Events (➪ page 21) signs and symptoms of the hepatitis C virus infection as well as known adverse effects due to medical therapy are summarized.

1.1 General considerations

Aim of this section is to summarize some general considerations about the infection with the hepatitis C virus, and provide necessary information for treatment decisions.

Epidemiology

Hepatitis C Virus (HCV) infection is one of the main causes of chronic liver disease worldwide with current estimates of approximately 130 – 210 million individuals (according to 3% of the world population) chronically infected with HCV[1,2]. Between 7.3 and 8.8 million persons are currently infected with HCV in the European Union. Overall HCV prevalence across Europe ranges between 0.4% and 3.5%, with wide geographical variation and higher rates in the south and the east.[3–5]

Hepatitis-C-Virus

HCV is a positive strand *Ribonucleic acid* (RNA) virus (genus of Hepacivirus, Flaviviridae family), characterized by high sequence heterogeneity[6]. Seven HCV genotypes, numbered 1 to 7, and a large number of subtypes have been described[7]. Genotype 1 is the most prevalent genotype worldwide, with a higher proportion of subtype 1b in Europe compared to 1a in the USA. Genotype 3a is highly prevalent in the European population of i.v. drug abusers. This group is currently experiencing an increasing incidence and prevalence of infections with HCV genotype 4. Genotype 2 is found in clusters in the Mediterranean region, while 5 and 6 are rare in Europe[8]. The novel genotype 7 was identified in patients from Canada and Belgium, possibly infected in Central Africa. The identification of HCV genotypes and subtypes is not only of epidemiological interest, but it determines the type and duration of antiviral therapy, including the risk of selecting resistance-associated variants during therapy.[3]

Routes of infection

Up to the 1990's the principal routes of HCV infection were blood transfusion, unsafe injection procedures, and intravenous drug use. The latter – facilitated by sharing paraphernalia, unstable housing, frequent cocaine use, and history of imprisonment – being the predominantly route in developed countries today. Other invasive behaviors, such as tattooing or acupuncture with unsafe materials, are also implicated in occasional HCV transmissions. The risk of perinatal and of heterosexual transmission of HCV is low, whilst male homosexual activity has become an important transmission route in Western countries.[6,9]

Fibrosis progression

In Europe, HCV infection is responsible for about 10% of cases of acute hepatitis. Acute hepatitis C is rarely severe, and symptoms occur in 10 to 50% of cases. Progression to persistent or chronic infection occurs in about three quarters of cases, is influenced by the IL28B genotype, and is associated with chronic hepatitis of a variable degree and with variable rates of fibrosis progression. On average, 10 to 20%

of patients develop cirrhosis over 20 – 30 years of infection.[4,10] Once at the cirrhotic stage, the risk of developing hepatocellular carcinoma is approximately 1 to 5% per year. Patients diagnosed with hepatocellular carcinoma have a 33% probability of death during the first year after diagnosis.[3,6]

Fibrosis co-factors

Cofactors known to be associated to fibrosis progression include older age at infection, male gender, chronic alcohol consumption, obesity, insulin resistance and type 2 diabetes, and immunosuppression (such as that occurring after solid organ transplantation and in untreated HIV infection)[11]. Tobacco smoking may increase inflammation and accelerate fibrosis[12]. Coffee consumption is associated with lower inflammatory activity, less advanced fibrosis and reduced risk of developing hepatocellular carcinoma[13]. The mainstay of HCV management is the modification of cofactors. An additional consideration is the fact that many of these cofactors also reduce the rate of response to interferon-based therapy.[3]

Aim of therapy

The primary goal of therapy is to eradicate HCV infection in order to prevent the complications of HCV-related liver and extrahepatic disease, including necroinflammation, fibrosis, cirrhosis, hepatocellular carcinoma, and death.[3,14,15]

Dual-therapy

Until 2011, the combination of peg-*Interferon* (IFN)-α and *Ribavirin* (RBV) (furthermore referred to as dual-therapy) was the approved treatment for chronic hepatitis C. With this regimen, patients infected with HCV genotype 1 had *Sustained Virological Response* (SVR) rates of approximately 40 – 50% in developed countries. Higher SVR rates were achieved in patients infected with HCV genotypes 2, 3, 5, and 6 (up to about 80%, and better for genotype 2 than for genotypes 3, 5, and 6) and intermediate SVR rates were achieved in those with HCV genotype 4.[3]

Triple-therapy

In 2011, *Telaprevir* (TVR) and *Boceprevir* (BOC) were licensed for use in HCV genotype 1 infection. These two drugs are first-generation *Direct-acting Antiviral Agents* (DAA)s, both targeting the HCV NS3/4A serine protease and thus referred to as protease inhibitor. Both TVR and BOC must be administered in combination with peg-IFN-α and RBV. These triple-therapy regimens have proven effective for treatment-naïve and for treatment-experienced patients, including previous null responders to dual-therapy.[16,17]

Sofosbuvir

In December 2013, the FDA approved the nucleotide analog inhibitor sofosbuvir for the treatment of chronic HCV infection in adults. Sofosbuvir can be used in combination with RBV for patients with genotypes 2 and 3, providing the first all-oral, interferon-free regimen for this disease. SVR at 12 weeks ranged from 89% to 95% for genotype 2 and 61% to 63% for genotype 3. Sofosbuvir can also be used in triple-therapy with peg-IFN and RBV for treatment-naïve patients with genotypes 1

and 4 (SVR-12 was 89%).[18–20]

Developing therapies

There are other DAAs at different stages of clinical development, some of them targeting HCV genotype 1 as well as other genotypes. Investigational drugs include second generation NS3/4A serine protease inhibitors, nucleoside/nucleotide and non-nucleoside inhibitors of the HCV-RNA-dependent RNA polymerase, and NS5A inhibitors. Additionally, host-targeting antiviral drugs, such as cyclophilin inhibitors, target host cell functions which are involved in the HCV life cycle. New therapeutic strategies aim towards higher efficacy, pan-genotypic activity, shortened treatment duration, easier administration and improved tolerability and patient adherence. It is probable that IFN-sparing and IFN-free regimens with or without ribavirin, which are being evaluated in clinical trials, will enter clinical practice in the next few years.[3,16]

1.2 Screening and treatment selection

The following section deals with the pre-treatment screening and the decision whether or not an antiviral therapy should be initiated and which therapy regime should be used.

1.2.1 Indications for treatment

Treatment indication

All treatment-naïve patients with compensated chronic liver disease related to HCV, who are willing to be treated and who have no contraindications to treatment, should be considered for therapy. Treatment should be scheduled, rather than deferred, in patients with advanced fibrosis (METAVIR[1] score F3 to F4) and in those patients with clinically significant extrahepatic manifestations.[3]

1.2.2 Diagnosis of acute and chronic hepatitis C

The diagnosis of acute and chronic HCV infection is based on the detection of HCV-RNA by a sensitive molecular method (lower limit of detection $< 15\,\mathrm{IU/ml}$). Anti-HCV antibodies are detectable by enzyme immunoassay in the vast majority of patients but may be negative in early acute hepatitis C and in profoundly immunosuppressed patients. Anti-HCV and HCV-RNA positivity does not differentiate acute hepatitis from exacerbation of chronic hepatitis C or from other causes in a patient with chronic hepatitis C.[3,6,14]

HCV-RNA positive
Anti-HCV neg.: early acute hepatitis C or profoundly immunodepressed patients
Anti-HCV pos.: acute or chronic hepatitis C depending on signs and symptoms and their time duration

Acute hepatitis C

The diagnosis of acute hepatitis C can be confidently made only if seroconversion to anti-HCV antibodies can be documented. About 50% of patients will be anti-HCV positive at diagnosis, thus acute hepatitis C can be suspected in occurrence of corresponding clinical signs and symptoms (alanine aminotransferase > 10 times the upper limit of normal, jaundice) in the absence of a history of chronic liver disease or other causes of acute hepatitis, or if a likely recent source of transmission is identifiable.[21,22]

Chronic hepatitis C

The diagnosis of chronic hepatitis C is based on the detection of both HCV anti-

[1] The METAVIR score is a system to quantify the degree of inflammation and fibrosis of a liver biopsy and ranges from F0 (no fibrosis) to F4 (cirrhosis).

bodies and HCV-RNA in the presence of signs of chronic hepatitis, either by elevated aminotransferases or by histology. Since spontaneous viral clearance is very rare beyond four to six months of infection, the diagnosis of chronic hepatitis C can be made after that time period.[22,23]

HCV-RNA negative
Anti-HCV pos.: following viral clearance (retest in a few weeks required)
Anti-HCV neg.: no infection verifiable

Following spontaneous or treatment-induced viral clearance anti-HCV antibodies persist in the absence of HCV-RNA but may decline and finally disappear in some individuals. Anti-HCV positive, HCV-RNA negative patients with acute hepatitis should be retested a few weeks later.[3,6]

1.2.3 Pretherapeutic assessment

Pretreatment assessment

Before institution of antiviral treatment a detailed assessment is required comprising the confirmation of a causal relationship between HCV infection and liver disease, valuation of liver disease severity, and determination of baseline virological parameters that will be useful to tailor therapy.[3]

Other causes of liver disease

A detailed medical and psychiatric history is essential, including complications of liver disease, presence of significant extrahepatic disease, and symptoms of chronic HCV that may impact on quality of life. The concomitance of other hepatotropic viruses (particularly *Hepatitis B Virus* (HBV)), past or ongoing psychiatric disorders, and possible co-morbidities, including alcoholism and/or substance use disorders, co-infection with *Human Immunodeficiancy Virus* (HIV), autoimmunity, genetic or metabolic liver diseases (for instance genetic hemochromatosis, diabetes or obesity) and the possibility of drug-induced hepatotoxicity should be assessed.[3,24]

Physical examination

A thorough physical examination should be performed since obesity, the metabolic syndrome, insulin resistance, and type 2 diabetes accelerate liver disease progression, increase the risk for the development of hepatocellular carcinoma, and reduce the response to the standard combination of peg-IFN/RBV.[3,25]

Liver disease severity

An assessment of liver disease severity is recommended prior to therapy. Identifying patients with cirrhosis is of particular importance, as the likelihood of response to therapy and post-treatment prognosis are proportional to the stage of fibrosis. Assessment of the stage of fibrosis by biopsy is not required in patients with clinical evidence of cirrhosis. Patients with likely cirrhosis need screening for hepatocellular carcinoma.

Table 1.1: Pretreatment assessments in patients with chronic HCV-infection[24]

	Necessary
☐	Medical history,
☐	Psychiatric history,
☐	Assessment of liver disease severity
☐	Serum Alanine Transaminase, albumin, and bilirubin (including direct bilirubin), and prothrombin time
☐	Hemoglobin, hematocrit, white blood count with differential, and platelet count
☐	Thyroidea stimulating hormone
☐	Serum creatinine
☐	Serum glucose
☐	Uric acid (while receiving TVR)
☐	Serum ferritin, iron saturation, and serum antinuclear antibodies
☐	Pregnancy test (in women in childbearing age)
☐	HIV serology
☐	Serum HBsAg, anti-HBc, anti-HBs, anti-HAV (total)
☐	Quantitative HCV-RNA measurement
☐	HCV genotype
☐	Previous antiviral therapies and response
☐	ECG in patients with preexisting cardiac disease
	Recommended
☐	Liver biopsy (if resuts will influence management; Alternative non-invasive fibrosis measurement - e.g. elastometry - can be performed.)
☐	IL-28B genotype (if results will influence management)
☐	Eye exam for retinopathy in patients with diabetes of hypertension
☐	Urine toxology sceen for opiates, cocaine, and amphetamines

Although liver biopsy remains the reference method non-invasive methods can be used instead to assess liver disease severity prior to therapy: Both liver stiffness measurement and biomarkers perform well in the identification of cirrhosis or no fibrosis but they perform less well in resolving intermediate degrees of fibrosis.[3]

HCV genotype

The HCV genotype must be assessed prior to treatment initiation and will determine the choice of therapy, the dose of RBV and treatment duration. In triple-therapy genotype 1a/1b subtyping provides relevant information with respect to different response rates and genetic barriers to resistance to protease inhibitors.[3,15]

Host genetics

IL28B genotyping may provide useful information for making clinical decisions in selected patients with genotypes 1 or 4. A favorable IL28B genotype (IL28B CC) identifies patients who are more likely to achieve a *Rapid virological response* (RVR) and who have a significant chance of cure with dual-therapy[26,27]. However, IL28B genotyping is not a prerequisite for treating hepatitis C.[3,28]

1.2.4 Contra-indications to therapy

Contra-indications

Contraindications to both dual- and triple-therapy are deduced from contraindications to antiviral medication and are given in table 1.2. Generally the same contraindications apply to TVR- or BOC-based triple-therapy as to dual-therapy.

Table 1.2: Contraindication to antiviral therapy for both dual and triple-therapy regimes.[3,29,30]

☐	Intolerance to antiviral drug or other ingredient.
☐	Uncontrolled depression.
☐	Psychosis or epilepsy.
☐	Pregnant women or couples unwilling to comply with adequate contraception.
☐	Newborn and children younger than 3 years old.
☐	Severe concurrent medical comorbidities, especially severe heart disease.
☐	Autoimmune-hepatitis.
☐	Severe liver dysfunction or decompensated liver disease (Child B,C).
☐	HIV-HCV-co-infection and liver cirrhosis with Child-Pugh ≥ 6.
☐	In combination with CYP3A-agents with low therapeutic index[a].

[a] applies for DAA since they are strong inhibitors of CYP3A thus leading to drug interactions.

However, the addition of DAAs to dual-therapy is associated with a significantly higher incidence of adverse events (especially hematological disorders and severe infections), thus the patient's adherence to therapy is crucial especially when triple-therapy is scheduled.[3] Treatment of patients with advanced liver disease whose parameters exceed label recommendations may be feasible in experienced centers under careful monitoring.

1.2.5 Medication

Antiviral agents shorten the clinical course, prevent complications, prevent latent and/or subsequent recurrences, decrease transmission, and eliminate established latency.[20] Current standard of care in the therapy of chronic HCV include Interferones, Ribavirin, and direct acting antivirals.[3,20,24,29–31]

Interferones

IFN

The type 1 IFNs (IFN-α/β) comprise a family of distinct proteins that are produced by a wide variety of cells, including fibroblasts, epithelial cells, and hepatocytes, although plasmacytoid dendritic cells are probably the major source in most viral infections.[30,31] In contrast, type II IFN (IFN-γ) is a single gene cytokine unrelated in structure to IFN-α/β that is produced largely by macrophages, natural killer cells, and T lymphocytes.[31]

Table 1.3: Interferones with therapeutical use in chronic hepatits C.

Generic (Tradename)	Characteristics
IFN-α-2b (Intron-A®)	IFN α-2b is a protein product manufactured by recombinant DNA technology. The adult dosage is 3 million units s.c. 3 times weekly. Modulation of host immune response by IFN may play an important role in the treatment of viral diseases.[20]
Peg-IFN-α-2a (Pegasys®)	peg-IFN α-2a consists of IFN α-2a attached to a 40-kd branched polyethylene glycol molecule. It is predominantly metabolized by the liver and excreted by the kidneys. The adult dosage is 180 μg/kg s.c. once weekly.[20]
Peg-IFN-α-2b (PegIntron®)	peg-IFN-α-2b consists of IFN-α-2b attached to a single 12-kd polyethylene glycol chain. The adult dose is 1.5 μg/kg s.c.. It is metabolized and excreted by the kidneys thus dosage adaption is necessary in patients with renal failure[20,29]
IFN-alfacon-1 (Inferax®)	IFN alfacon is a protein product synthesized by combining the most common amino acid sequences from all 12 naturally occurring IFNs. The adult dosage is 9 μg s.c. 3 times weekly.[20,29]

The α- and β-types of IFN have been approved for use in the treatment of chronic HCV. IFN-α preparations come in non-pegylated and pegylated forms, depending on whether polyethylene glycol has been attached.[32] As a result pegylation increases the serum half life 10 times compared to the 2 – 4 hour half life of non-pegylated interferone.[33] Peg-IFN has sustained absorption, a slower rate of clearance, and a longer half-life than unmodified IFN, which enables a more convenient once-weekly dosing and significantly improves quality of life for patients.[20]. Interferones must be administered subcuteneously.

Infected cells produce and excrete IFN which consecutively develop an antiviral effect due to depletion of ribosomal RNA and messenger RNA thus killing infected cells, and receptor induced inhibition of protein-synthesis (RNA-transcription) thus

protecting nearby non-infected cells.[30]

Common adverse effects to all interferones are flu-like symptoms like fatigue, fever, myalgia, and cephalea.[29]

Ribavirin

RBV

RBV (Rebetol®, Virazole®, Copegus®) is an antiviral nucleoside analogue which inhibits the replication of RNA- and DNA-viruses[30,33] with a mild, transient antiviral effect on HCV replication when administered as mono-therapy[20,34]. In combination with IFN RBV improves SVR rates by approximately 25 – 30%. The addition of RBV to DAA reduces viral *Breakthrough* (BT) and/or relapses, particularly in patients harboring HCV subtype 1a[34]. RBV is absorbed via mucosa and excreted by the kidneys with a serum half life of 9 hours[30]. Proposed mechanisms of action for RBV against HCV include,[30,33,34]

- a direct effect against the HCV-RNA dependent RNA-polymerase,
- induction of misincorporation of RBV-nucleotides into viral RNA leading to lethal mutagenesis,
- depletion of intracellular pools via inhibition of inosine monophosphate dehydrogenase,
- alteration in the cytokine balance between a Th2 profile (anti-inflammatory) to a Th1 profile (pro-inflammatory), and
- potentiating the effect of interferon via up-regulation of genes involved in interferon signalling.

RBV has teratogenetic effects. Common advances effects are fatigue, cephalea, myalgia, nausea, psychiatric disorders, gastrointestinal disfunction, and anemia.[29]

Direct acting antivirals

NS3/4A Protease Inhibitors

NS3/4A protease inhibitors interfere with the ability of HCV to replicate by covalently and reversibly inhibiting HCV NS3/4A protease needed for proteolytic cleavage of the HCV-encoded polyprotein into mature forms, thus inhibiting viral replication[20]. NS3/4A inhibitors are indicated for chronic HCV genotype 1 (1a in case of Simeprevir) infection in combination with peg-IFN-α and RBV.[3,20]

NS5B Polymerase Inhibitors

NS5B polymerase inhibitors interfere with the viral enzyme NS5B by incorporating the active component into the viral RNA, which results in the suppression of HCV replication and interruption of HCV life cycle.

Table 1.4: Direct acting antivirals with therapeutic implication to chronic hepatitis C.

Generic (Tradename)	Characteristics
Boceprevir (Victrelis®)	NS3/4A protease inhibitor. The recommended standard dosage is 800 mg orally 3 times daily together with food. BOC is a strong inhibitor of CYP3A4/5 and may produce considerable drug interactions. Common adverse effects of BOC include fatigue, anemia, nausea, cephalea, and dysgeusia.[20]
Telaprevir (Incivo®)	NS3/4A protease inhibitor. The recommended standard dosage is 750 mg orally 3 times daily together with food (containing at least 20 g fat)[3], though recently presented clinical trial data showed that 12-hourly dosing (1125 mg 12 hourly) does not have inferior efficacy in comparison with the licensed schedule (750 mg 8 hourly)[20]. TVR is a strong inhibitor of CYP3A4/5 and may produce considerable drug interactions. Common adverse effects of TVR are anemia, rash, thrombozytopenia, lymphopenia, pruritus, and nausea.
Simeprevir (Olysio®)	NS3/4A protease inhibitor. Contrary to other protease inhibitors, Simeprevir is administered once a day together with food. Simeprevir has teratogenetic effects and is metabolized through CYP3A. Common adverse effects are rash, pruritus, nausea, and photosensibility.[20]
Sofosbuvir (Sovaldi®)	NS5B polymerase inhibitor. It is indicated for treatment of HCV genotypes 1, 2, 3, and 4 as part of a combination antiviral regimen, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) to prevent HCV recurrence and those with HCV/HIV-1 co-infection.[20] Sofosbuvir is administered once a day independent of meal. Common adverse effects are fatigue, cephalea, nausea, sleeping disorders, and anemia.

1.2.6 Treatment decision

Currently dual- and triple-therapy regimes are available in the treatment of chronic hepatitis C. Treatment decision and probability of SVR are primarily deduced from HCV-genotype[6]. The patients therapy experience (naïve vs. experienced) and presumable adherence to antiviral therapy are additional factors[35]. The latter is of particularly importance when triple-therapy is intended, since due to higher rates of discontinuation because of adverse events, noncompliance to the therapy regime may induce resistances.[24] Therapy experienced patients have failed to eradicate HCV on

prior therapy and can be classified into virological relapsers, partial responders, or null responders due to their virological response to therapy.[3] The previous response to IFN-based therapy is an important predictor of success of triple-therapy, with relapsers having higher cure rates than partial responders, who in turn have higher cure rates than Null responders (*Null response* (NR)). However, a considerable proportion of patients with a history of peg-IFN/RBV treatment failure do not have a precise record of their modality of non-response.[3]

Triple therapy

Genotyp 1

The current standard of care for therapy-naïve and therapy-experienced patients with chronic HCV genotype 1 is triple-therapy comprising either of the pegylated IFN-αs (α-2a or α-2b) and RBV with either of the DAAs (BOC or TVR)[3,20,24,32], since triple-therapy regimens significantly improve SVR rates in patients with HCV genotype 1 compared to peg-IFN/RBV dual-therapy.[3,20,36].

There is no head-to-head comparison to allow recommendation of BOC or TVR as preferred therapy.[3] On the basis of the TVR adverse effect profile, BOC in combination with peg-IFN/RBV may be more appropriate in patients with skin disorders (e.g. psoriasis) or gout.[24]

The benefits of triple-therapy over dual-therapy are observed for patients with prior relapse, partial response and null response patterns of failure[3], thus patients infected with HCV genotype 1 who failed to eradicate HCV on prior dual-therapy with IFN and RBV should be considered for treatment with triple-therapy. In this setting, triple-therapy yields SVR rates of 29 – 88%, depending on the type of previous non-response and on the stage of liver disease.[3]

Selected patients with high likelihood of SVR to peg-IFN/RBV or with contraindications to BOC or TVR can be treated with dual-therapy[3] However, patients failing to respond to BOC should not be retreated with TVR or vice versa[3], thus re-treatment of triple-therapy experienced patients infected with genotype 1 can only be done through dual-therapy.

Dual therapy

Genotype 1

In genotype 1 patients dual-therapy may be appropriate for selected treatment-naïve

patients with baseline features predicting a high likelihood of RVR and SVR to peg-IFN/RBV. Cost savings and better tolerability of dual-therapy must be taken into account. Moreover, occasional patients may have co-morbid conditions that require medication known or predicted to have adverse drug-drug interaction with the first-generation DAA. In HCV genotype 1 patients with the favorable IL28B genotype (IL28B CC), dual-therapy obtained similar SVR rates to triple-therapy including BOC.[3]

Genotyp 2 – 6

In patients infected by HCV genotype 2, 3, 4, 5, or 6, the standard of care regimen consists of the combination of either of the two pegylated IFN-αs with RBV[3]. In therapy naïve patients SVR rates for genotype 1 are 40 – 50% and for genotype 2 or 3 up to 80%.[6]

HCV genotype 1 patients who fail to achieve SVR with peg-IFN/RBV have a small likelihood of achieving an SVR when re-treated with the same drugs at the same doses.[3] Patients with HCV genotypes other than 1 who have failed previous IFN-α-based treatment, with or without RBV, can be considered for re-treatment with peg-IFN/RBV depending on careful assessment of factors such as adequacy of prior treatment and stage of liver disease.[3]

Table 1.5: Treatment options depending on HCV genotype and treatment experience (naïve vs. experienced).

Genotype	Treatment experience	Treatment options
1	naïve	peg-IFN/RBV + BOC or TVR, response guided therapy possible
		peg-IFN/RBV, if triple-therapy is unavaliable, contraindicated, or not indicated, response guided therapy possible
2 – 6	naïve	PegIFN/RBV, response guided therapy possible
1 – 6	experienced	PegIFN/RBV, responce guided therapy not recommended

1.3 Treatment

A brief discussion of goals and endpoints of HCV therapy, dosage of antiviral medication, treatment process and duration and follow up after end of treatment.

1.3.1 Goals and endpoints of hepatitis C antiviral therapy

Goals

The primary goal of therapy is to eradicate HCV infection in order to prevent complications of HCV-related liver and extrahepatic disease. When HCV is eradicated, necroinflammation ceases and fibrosis progression is halted in non-cirrhotic patients. In patients with cirrhosis, HCV eradication reduces the rate of decompensation and will reduce, albeit not abolish, the risk of hepatocellular carcinoma[3,22].

Endpoint

The endpoint of therapy is SVR, defined by undetectable HCV-RNA 24 weeks after the end of therapy (SVR-24), as assessed by a sensitive molecular method with a low limit of detection $< 15\,\mathrm{IU/ml}$.[3,22,24] Once obtained, SVR usually corresponds to a definitive cure of HCV infection in more than 99% of patients[37]. However, undetectable HCV-RNA at 12 weeks after the end of therapy (SVR-12) may be used as prognostic marker, since the concordance with SVR-24 is 99%.[3,38]

Intermediate endpoints

Intermediate endpoints are used during therapy to assess the likelihood of SVR and tailor treatment duration. They include HCV-RNA level measurements at 4, 12, and 24 weeks of therapy, which are interpreted in comparison to the baseline HCV-RNA level.[22]

1.3.2 Dosage of antiviral medication

Dosage

Initial dosage depends primarily on HCV genotype. The concomitance of a high body mass index and/or baseline factors suggesting low responsiveness to antiviral therapy (insulin resistance, metabolic syndrome, severe fibrosis or cirrhosis, old age) influence the dosage of antiviral medication. However, the dosage of peg-IFN and RBV must be modified due to renal impairment, dose adjustments of BOC and TVR is not necessary for renal or hepatic impairment (Child-Pugh < 7)[3]. Recommended dosage for antiviral therapy is given in table 1.6.

Table 1.6: Dosage of antiviral treatment for chronic hepatitis C in adults[3,20,24,29]. RBV is administered in two divided doses daily, DAA's are administered every 7 – 9 h with food (at least 20 g fat in case of TVR).

Generic	Approved for genotype	Recommended dose
PegIFN-α-2a[a]	1 – 6	180 μg/week s.c.
PegIFN-α-2b[b]	1 – 6	1.5 μg/kg/week s.c.
RBV[c]	1	*in combination with peg-IFN-α2a* 1 000 mg/die p.o. ($\leq$ 75 kg body weight) or 1 200 mg/die p.o. ($>$ 75 kg body weight)
	1	*in combination with peg-IFN-α2b* 800 mg/die p.o. ($<$ 65 kg body weight) or 1 000 mg/die p.o. (65 – 85 kg body weight) or 1 200 mg/die p.o. (85 – 105 kg body weight) or 1 400 mg/die p.o. ($>$ 105 kg body weight)
	2 or 3	800 mg/die p.o. (with risk factors) or
	2 or 3	15 mg/kg/die p.o. (without risk factors)
	4, 5, 6	15 mg/kg/die p.o.
BOC	1	800 mg/8 h p.o.
TVR	1	750 mg/8 h p.o.

[a] reduce to 135 μg/week s.c. in case of Clcr $<$ 30 ml/min or hemodialysis.
[b] reduce by 25% if Clcr 30 – 50 ml/min; reduce by 50% if Clcr 10 – 29 ml/min.
[c] 200 mg/die p.o., alternating with 400 mg/die p.o. if Clcr 30 – 50 ml/min; 200 mg/die p.o. if Clcr $<$ 30 ml/min.

1.3.3 Treatment efficacy and safety monitoring

Efficacy and safety

Monitoring treatment efficacy and safety is crucial to patients adherence, which itself is an important parameter for SVR and therapy success. Monitoring of treatment efficacy is based on repeated measurements of HCV-RNA levels, while monitoring of treatment safety is done by recurring assessment of clinical side effects (such as weight loss, fever, severe fatigue, depression, irritability, sleeping disorders, skin reactions, and dyspnoea, compare Table 1.12) and blood analysis (e.g. differential blood count, TSH, electrolytes, compare Table 1.1).[3] Recommended treatment monitoring is summarized in table 1.7.

Table 1.7: Treatment efficacy and safety monitoring.[3] BL, baseline (representing week of therapy 0); EOT, end of treatment.

	week of therapy						follow up	
	BL	4	8	12	24	EOT	12	24
HCV-RNA								
dual-therapy	☐	☐		☐	☐	☐	☐	☐
triple-therapy (BOC)[a]	☐	☐	☐	☐		☐	☐	☐
triple-therapy (TVR)	☐	☐		☐	☐	☐	☐	☐
Clinical exploration	Assess for clinical side effects at each visit.							
Differential blood count	at weeks 1, 2, 4 and every 4 – 8 weeks thereafter.							
TSH	TSH every 12 weeks of therapy.							

[a] for BOC therapy, here and elsewhere in this thesis, the timing of RNA quantitation refers to weeks after commencement of the dual-therapy lead-in.

1.3.4 Treatment duration

Response-guided therapy

Treatment duration depends on HCV genotype and the patients therapy experiences and can be tailored to the on-treatment virological response.[39] The likelihood of SVR is directly proportional to the speed of HCV-RNA disappearance, thus upon treatment, HCV-RNA levels should be assessed at baseline and weeks 4 and 12, regardless of the HCV genotype.[3,29]. With response guided therapy overall treatment duration can be abbreviated.

Dual therapy

With dual-therapy, treatment should only be abbreviated if the baseline HCV-RNA level is less than 400 000 IU/ml, an RVR is achieved and no further negative predictor of response (i.e. advanced fibrosis/cirrhosis, metabolic syndrome, insulin resistance, hepatic steatosis) is present.[3] Dual-therapy duration should be tailored to the on-treatment virological response at weeks 4 and 12.[3]Patients with HCV genotype 1 have a much less favorable response to therapy and are treated for 48 weeks, compared with patients infected with genotypes 2 and 3, in whom a 24-weeks course of therapy is sufficient.[20,40] The current standard-of-care therapy duration for HCV genotypes 4, 5 and 6 is 48 weeks. A shorter course with 24 weeks of therapy may be considered for patients with genotype 6.[3,41]. In therapy-experienced patients with cirrhosis an inferior outcome was found in all treatment groups and response-guided therapy is not recommended for cirrhotic patients, irrespective of the prior treatment response to dual-therapy. If the pattern of prior response to dual-therapy is not clearly documented, the patient should not be treated with abbreviated response-guided therapy.[3]

Table 1.8: Overall treatment duration in dual and triple-therapy regimens.[3,24,29] GT, genotype; LVL, low viral load at baseline (< 400 000 – 800 000 IU/ml); HVL, high viral load at baseline (> 400 000 – 800 000 IU/ml); RVR, rapid viral response (HCV-RNA not detectable at week 4 of therapy).

Regime	**Criteria**	**Treatment duration**
Dual therapy	*therapy-naïve*	
	GT 1, LVL, RVR	24 weeks
	GT 1, HVL	48 weeks
	GT 1, non-RVR	48 – 72 weeks
	GT 2,3, LVL, RVR	16 weeks
	GT 2,3, risk factors, non-RVR	48 weeks
	GT 4,5	48 weeks
	GT 6	24 weeks
	therapy-experienced	
	GT 1 – 6	48 – 72 weeks
Triple therapy (BOC)	GT 1 naïve or relapsers without cirrhosis, *Early response* (ER)	28 weeks
	GT 1, naïve or relapsers with cirrhosis, *Partial response* (PR), NR, *Late response* (LR)	48 weeks
Triple therapy (TVR)	GT 1, naïve or relapsers without cirrhosis, eRVR	24 weeks
	GT 1, naïve or relapsers with cirrhosis, PR, NR	48 weeks

An extended treatment duration may be beneficial in selected patients.[42]

Therapy regimen containing BOC is initiated by a 4 week lead-in with peg-IFN-α/RBV dual-therapy, followed by peg-IFN-α/RBV/BOC triple-therapy.[43] Patients who are HCV-RNA undetectable at week 8 and remain undetectable at week 24 can stop all drugs at week 28. Patients with detectable HCV-RNA at any time point between week 8 and 24, should continue triple-therapy until week 36, then BOC should be stopped and peg-IFN-α/RBV continued until week 48. In the presence of cirrhosis, the recommended treatment schedule is a 4 week lead-in phase of peg-IFN-α/RBV followed by 44 weeks of peg-IFN-α/RBV plus BOC.[3,15] BOC

With triple-therapy containing TVR the DAA in combination with peg-IFN-α/RBV is administered for 12 weeks, followed by peg-IFN-α/RBV dual-therapy until week 48.[44] Overall treatment duration can be shortened to 24 weeks in naïve patients with an eRVR, while treatment needs to be continued until week 48 in those without an eRVR. In patients with cirrhosis, treatment with peg-IFN-α/RBV is to be continued TVR

until week 48 regardless of HCV-RNA kinetics.[3,15]

1.3.5 Treatment dose reductions

Peg-IFN-α dose should be reduced in case of severe side effects, such as clinical symptoms of severe depression, if the absolute neutophilia count or the platelet count falls below their threshold levels, and/or in case of progressive elevation of alanine transaminase (see Table 1.9). In case of deterioration either of side effects and/or laboratory values peg-IFN-α should be stopped. When neutrophilia or platelet counts rise from those nadir values and/or side effects decay, treatment can be restarted, but at a reduced dose.[3,29] IFN

Table 1.9: General rules for upon treatment dose modification.[3,24,29] IFN, Interferone; RBV, Ribavirin; DAA, direct action antivirals; ALT, alanine transaminase; Hb, hemoglobin.

Generic	**Criteria**	**Recommended dose reduction**
IFN	Severe depression, Neutrophil count $< 750/\mu$l, Platelet count $< 50\,000/\mu$l, Progressive elevation of ALT.	Peg-IFN-α-2a: reduce to 135/90/45 μg/week s.c. Peg-IFN-α-2b: reduce to 1.0/0.5 μg/kg/week s.c.
	Marked depression, Neutrophil count $< 500/\mu$l, Platelet count $< 25\,000/\mu$l, Severe elevation of ALT, bilirubin.	Peg-IFN-α should be stopped
	If neutrophil count rises again (e.g. $> 1\,000/\mu$l)	Restart peg-IFN-α with reduced dose.
RBV	Anemia (Hb < 10 g/dl)	reduce by 200 mg at a time
	Anemia (Hb < 8.5 g/dl)	RBV should be stopped
	If Hb normalize	Restart RBV with reduced dose
DAA	dose reduction is nor recommended (either stopped or continued at initial dose)	

RBV dose should be reduced if significant anemia occurs and should be stopped if hemoglobin level falls below 8.5 g/dl. Alternatively, the use of growth factors may reduce the need to reduce RBV dose and high doses of both peg-IFN-α and/or RBV can be maintained.[45]If hemoglobin rises to normal values after RBV has been stopped, treatment can be restarted, but at reduced dose.[29] RBV

BOC or TVR dose should not be reduced during therapy, as this will favor the DAA

development of antiviral drug resistance. The DAAs should either by stopped completely, because of side effects, or be continued at the same dose provided that adjuvant therapy is prescribed. Once TVR has been stopped, it should never be reintroduced. However, hemoglobin decline is accelerated by the addition of first generation DAA to peg-IFN/RBV, RBV dose reduction should be the initial response to significant anemia.[3]

Anyway treatment should be stopped in case of severe adverse events including hepatitis flair (alanine transaminase levels above 10 times normal), acute hepatic decompensation, severe bacterial infection at any site, and/or achievement of a futility criteria.[3,24]

Treatment stop

1.3.6 Treatment response and futility criteria

The likelihood of SVR is directly proportional to the speed of HCV-RNA disappearance thus stopping rules for futility are recommended upon therapy (see Table 1.10).

Table 1.10: Futility criteria for dual and triple-therapy.

	Dual therapy
☐	HCV-RNA decrease is less than $2\,\log_{10}$ at week 12 of therapy,[3]
☐	HCV-RNA is detectable at week 24 of therapy.[3]
	Triple therapy (BOC)
☐	HCV-RNA > 100 IU/ml at week 12 of therapy[3,24],
☐	HCV-RNA detectable at week 24[3,24], and
☐	in case of viral BT later on[3], as well as
☐	HCV-RNA rebounds at any time-point ($\geq 1\,\log_{10}$ increase from the nadir HCV-RNA)[24].
	Triple therapy (TVR)
☐	HCV-RNA > 1000 IU/ml at week 4 or 12 of therapy[3,24], and
☐	in case of BT later on[3], as well as
☐	HCV-RNA detectable at week 24[24], and
☐	HCV-RNA rebounds at any time-point ($\geq 1\,\log_{10}$ increase from the nadir HCV-RNA)[24].

With dual-therapy patients with detectable HCV-RNA at week 24, there is a very small chance of SVR ($1-3\%$) and treatment should be stopped. The stopping rules for futility are identical to those applied in treatment-naïve patients for both TVR and BOC.[3] If viremia is present after 6 months, additional therapy has a negligible incremental benefit, and treatment should be stopped in all patients regardless of the viral genotype. With HIV co-infection, all patients with a response to therapy at

the end of 6 months should receive an additional 6 months of combination therapy regardless of the genotype.[20]

1.3.7 End of treatment and follow-up

During follow-up patients safety monitoring must be continued, comprising clinical assessment and laboratory analysis (compare to Table 1.7). The end-of-treatment virological response and the SVR at 24 weeks after the end of treatment must be assessed. Additionally the SVR at week 12 after end of treatment can be assessed. Non-cirrhotic patients who achieve an SVR should be retested for HCV-RNA at 48 weeks post-treatment. If HCV-RNA is still not detected, the infection can be considered as definitely eradicated and HCV-RNA need not be retested.[3]

1.4 Clinical presentation and adverse events

Signs and symptoms of the HCV infection as well as known adverse effects due to medical therapy are summarized.

Signs and symptoms can be related to the underlying hepatitis or appear as adverse effect due to medication. The appearance of adverse effects as well as their severity generally depends on the therapy regime, dosage of medication, and route of administration. Since adverse effects directly relate to quality of life and thus influences the patients adherence to the antiviral therapy[46], early recognition and immediate treatment are crucial for the success of antiviral therapy.

Acute hepatitis

Within the first week after infection the clinical presentation is dominated by flu-like symptoms including moderate fever, abnormal fatigue, arthralgia, myalgia, and gastrointestinal symptoms like nausea, emesis, diarrhoe, absence of appetite, and upper abdominal pain. In the following 4 – 8 weeks clinical signs are predominantly caused by actual hepatic damage, including darkening of urine (bilirubinuria), discoloration of stool, significant elevation of alanine transaminase, aspartate transaminase, and bilirubin within blood serum. Pruritus, hepato- and splenomegalia, and jaundice are late onset signs and may diminish with the progression of hepatitis. However, abnormal fatigue may be present the following weeks to months.[6,21]

Chronic hepatitis

At low inflammatory activity, the liver is not enlarged and usually there are no complaints expressed. For moderate or severe inflammatory activity the patient suffers from strong reduction in performance and fatigue associated with loss of appetite. The enlargement of the liver leads to an abdominal discomfort in the upper right abdomen. Discoloration of the urine and appearance of jaundice and skin signs of liver disease may be present. In 30% of cases a splenomegaly may accompany.[6]

Dual-therapy

In dual-therapy adverse effects are generally induced by IFN. The most frequently adverse effects are fever, shivering, fatigue, cephalea, nausea, emesis, arthralgia, myalgia, depressions, alterations of the skin, alopecia, neutropenia, and anemia.[30,47–55] Flu-like symptoms are often present after peg-IFN-α injections. They are easily controlled by paracetamol and tend to attenuate after 4 – 6 weeks of therapy.[3] Rare but severe adverse effects include hypo- or hyperthyreodism, exacerbation of a preexisting autoimmune disorder, retinopathia, and severe depressions[33]. Commonly the addition of RBV aggravates those adverse effects, particularly flu-like symptoms and hematological side effects including neutropenia, anemia, thrombocytopenia and lymphopenia.[3,30] There is no evidence that neutropenia during peg-IFN /RBV therapy is

associated with more frequent infection episodes.[3]

Table 1.11: Frequently abnormal laboratory values during dual-therapy[29].

elevated: Alanine transaminase, bilirubin, triglyceride, hyperthyreoidism
reduced: Hypokalemia, hypocalcemia, hypophosphatemia, leukopenia, neutropenia, lymphopenia, thrombozytopenia, anemia, hypothyreoidism

Triple-therapy

The addition of DAA agents to IFN and RBV is associated with an increased incidence of adverse events, requiring discontinuation of the DAA agent in 10% – 21% of patients (reviewd in[24]). Adverse events with increased frequency include anemia (both BOC and TVR, especially in patients with liver cirrhosis) thrombozytopenia (TVR), lymphopenia (TVR), nausea (both), neutropenia (BOC), dysgeusia (both), gastrointestinal upset (both), fatigue (both), rash (TVR), cephalea (BOC), pruritus (TVR), and perianal discomfort (TVR). A rare but severe adverse effect with TVR is Stevens-Johnson-Syndrom.[3,24,36,48,56] However, an increased incidence of infectious adverse effects was found in triple-therapy.[17,57]

Table 1.12: Incidence of adverse events. Given are adverse events with a single incidence higher $\geq 10\%$ reporter for either of the drugs. Incidences summarized from adverse events provided by MedScape Reference[58–62].

Adverse events	BOC	TVR	RBV	Pegasys	PegIntron
Abdominal pain				8% – 26%	15%
Alopecia	22 – 27%		27 – 32%	18% – 28%	22%
Anemia	45 – 50%	36%	10 – 36%	2% – 14%	
Anorectal discomfort		11%			
Anorexia	25%		21 – 27%		20%
Anxiety/irritability	21 – 22%		23 – 32%	19% – 33%	28%
Arthralgia	19 – 23%		29 – 33%	22% – 28%	
Asthenia	15 – 21%				
Chills	33 – 34%				
Cough				4% – 10%	
Decreased white blood count			5 – 11%		
Depression			23 – 36%	18% – 20%	16 – 29%
Dermatitis				8% – 16%	7%
Diarrhea	25%	26%		11% – 31%	18%
Dizziness	16 – 19%		17 – 26%	13% – 23%	12%
Dry skin	18 – 22%			4% – 10%	11%
Dysgeusia	35 – 44%		6 – 8%		
Dyspepsia			14 – 16%		6%
Dyspnea	8 – 11%		17 – 19%	4% – 13%	
Emotional lability			7 – 12%		
Fatigue	55 – 58%	56%	60 – 70%	24% – 67%	52%
Feeling nervous				19% – 33%	
Fever			32 – 41%	24% – 54%	22%
Flu-like syndrome			13 – 18%	25% – 47%	
Headache	>35%		63 – 66%	27% – 54%	56%
Hemolysis			61 – 64%		
Hemorrhoids		12%			
Hyperbilirubinemia			24 – 34%		
Impaired concentration			10 – 14%	8% – 10%	5 – 12%
Injection site reaction				10% – 31%	47%
Insomnia	30 – 34%		26 – 39%	19% – 30%	23%
Loss of appetite				16% – 24%	
Lymphocyte count abnormal				3% – 14%	
Musculoskeletal pain			20 – 28%		
Myalgia			61 – 64%	26% – 51%	
Nasal congestion			13 – 18%		
Nausea and vomiting	15 – 46%	13 – 39%	9 – 47%	5% – 25%	7 – 26%
Neutropenia	14 – 25%			21% – 40%	
Pain					12%
Pharyngitis					10%
Pruritus		47%	13 – 21%	12% – 19%	12%
Rash	16 – 17%	56%	20 – 28%	5% – 8%	6%
Rigor			40 – 43%	25% – 47%	
Sinusitis			9 – 12%		7%
Thrombocytopenia			6 – 14%	5% – 8%	
Increase in transaminases					10%
Weakness			9 – 10%		
weight loss				4% – 16%	11%
Xerostomia	11 – 15%				

2 Methods

A description of used methods:

This chapter starts with **Subjects and ethical considerations** (➪ page 25), a summary of inclusion ad exclusion criteria and ethical and gender aspects.

Subsequently **Study design** (➪ page 25) briefly describes the retrospective character of the thesis' study and defines the included cohorts.

The aim of **Data collection and protection** (➪ page 26) is to acquire necessary data from the patient's health record and to assure a proper data privacy.

In **Endpoints and hypothesis** (➪ page 26) a brief discussion about the study's primary and secondary endpoints as well as the primary hypothesis is given.

At last **Data abstraction and statistical analysis** (➪ page 27) elucidates how collected data is processed and which statistical tools are used.

2.1 Subjects and ethical considerations

Criteria for subject inclusion and exclusion as well as ethical considerations are described.

Included patients

All patients chronically infected with hepatitis C virus who received antiviral treatment at the clinic for liver disease at the Department of gastroenterology and hepatology, Medical University Graz, were evaluated to be included in this thesis.

To stay up-to-date with respect to current guidelines and to acquire comparable data patients were included if their antiviral treatment was initiated between January 2011 and June 2013 and who are treated according the guidelines of the European Association for the Study of the Liver[22,24] and/or within any clinical trial based on peg-IFN-α and RBV with or without either BOC or TVR.

Excluded patients

Patients were excluded if they were treated either by the use of another antiviral medication or if their treatment protocol did not follow current guidelines. These were expected to be patients within other clinical trials.

Retrospective design

Due to the retrospective design of this study there is no direct interaction with the patients. However, the progress of this study did not influence ongoing treatment. As HCV affects both female and male gender, the results of this thesis applies to both genders in equal shares.

Ethics committee

The Ethics committee, Medical University Graz, has determined that the study protocol adheres to ethical principles and therefore has approved this thesis' study.

2.2 Study design

The design of this thesis' study and the definition of the study cohorts.

The present thesis based on a retrospective cohort study. Cohorts are patients treated with antiviral dual-therapy (combination of any peg-IFN-α and RBV) and patients treated with antiviral triple-therapy (combination of any peg-IFN-α and RBV in addition with either BOC or TVR).

A total of 60 data sets per cohort were expected. Due to the descriptive character of this study a random number planning was omitted.

2.3 Data collection and data protection

The patient's health records are the fundamental of data acquisition.

Data collection

The patient's data was collected using clinical records, patient history, laboratory and genetic data, and – if available and no exclusion criteria were met – information from other clinical trials. Data was acquired from both handwritten and/or printed as well as electronic health records. Data was collected unaltered (i.e. in boolean, number, float, or in text format in lack of a bijective correspondence) within a spreadsheet (Libre-Office Version 3.6.2.2) and stored on a computer with limited access. Only authorized people has access to the original data.

Data protection

Patients are identified with a patient-code and consecutively numbered. There is no designed order within the therapy regimes since patients are included in sequence of the availability of their health record. Thus, the patient within dual therapy whose health record was accessed first was referred to "Dual001". Consecutively, patients whose health records were accessed later on were referred to "Dual00x" with x being an ascending number. A respective approach was used for patients within triple therapy regimes, i.e. "Triple00x".

2.4 Endpoints and hypothesis

Discussion of the primary and secondary endpoints ant the study's primary hypothesis.

Primary endpoint

The primary hypothesis is to verify if there is a higher incidence of severe infectious adverse events in triple-therapy compared to dual-therapy. Thus primary endpoint is the number of infections and infestations with dual- and triple-therapy.

Secondary endpoints

Secondary endpoints are other adverse events[22,24,32,36,46–51,63] and continuous recorded data during the treatment period (compare Table 2.1 and Table 2.2) always with respect to the chronology treatment progression.

Table 2.1: Primary and secondary endpoints of the thesis' study.

Demographic data:	Age, gender, body weight, body height.
Patient's history and medication:	Pre-existing- and Co-morbidity, in particular known risk factors (e.g. alcohol abuse, smoking, diabetes, hepatitis evoked by others than HCV).
Antiviral medication:	Current specialty and dose, as well as outcome of previous antiviral therapy.
Laboratory data:	Blood count, alanine transaminase, aspartate transaminase, GGT, AP, bilirubin, albumin, PT, INR, electrolytes, creatinin, TSH, glucose, urea, ferritin, ANA, HCV-genotype, host IL-28-genotype, HCV-RNA, HIV, HAV-antibody, HBs-antibody, HBs-antigen, HBc-antibody.
Adverse events:	A detailed list of adverse events is given in Table 2.2

2.5 Data abstraction and statistical analysis

A description about how the collected data is processed and which statistical tools are used.

Data analysis

Data analysis was done by means of descriptive statistics. A data abstraction form was created based on data elements captured in previous studies[22,24,32,36,46–51,63].

Included time-points are the ward round at the patients screening (during screening the patient is evaluated if an antiviral treatment is applicable or not), baseline, during treatment, and 12 and 24 weeks of follow up. Therefore all clinical contacts to the patient in the time between a few weeks before treatment started until a few months after antiviral treatment has stopped have been evaluated.

If no baseline date was documented, the date of the first application of any antiviral medication was used instead. Similarly, in lack of a documented *End Of Treatment* (EOT) the latest date of antiviral medication application was used. In lack of essential data (e.g. no HCV-RNA determination at EOT) the chronology closest available data was used instead.

Adverse event classification

Adverse events was classified according to CTCAE[1 63] in System Organ Classes and

[1]CTCAE: Common Terminology Criteria for Adverse Events, U.S. department of health and human services, Version 4.03, 2010

Adverse Event Terms (see Table 2.2). The CTCAE graduation of the severity of adverse events was not possible due to the fragmentary documentation: if severity was documented the graduation was rather imprecise.

Acquired adverse events were screened leading to more than 1 500 used phrases. These were summarized into adverse event terms and furthermore classified into organ systems (see Table 2.2 and Appendix 6.3).

A total of 120 data sets was expected (including both dual- and triple-therapy patients). Descriptive statistics for continuous data was summarized as means $\pm$ standard deviations. For non-normal distribution median and quartiles were used. Categorical data was given in absolute and/or relative frequencies. Variables are tested for normal distribution using the Kolmogorov-Smirnov test.

R, version 3.0.2 (Frisbee Sailing, 2013-09-25, The R Foundation for Statistical Computing) was used for linear and multiple regression analysis, including Pearsons correlation coefficient, for Students t-test for independent means, and to assess the significance of the difference between two correlation coefficients. Significance was accepted when p-values < 0.05.

Table 2.2: Classification of adverse events based on the CTCAE-classification[63]. A detailed listing of adverse events classification and original german adverse event terms is given in Appendix 6.3.

System organ class	Adverse event term example
Blood and lymphatic system disorders	Anemia, leukopenia, neutropenia, lymphopenia
Cardiac disorders and Vascular disorders	Hypertension, hypotension, circulatory weakness, nycturia
Ear and labyrinth disorders	otitis, acute hearing loss
Eye disorders	burning eye, dry eye, acute disturbance of vision, conjunctivitis, bleeding
Fluid shift	peripheral edema, swelling, pleural effusion
Gastrointestinal disorders	diarrhoe, nausea, emesis, loss of appetite, gastralgia, dyspepsia, abdominal pain, gastroenteritis, intestinal discomfort, provtitis, colitis, gastrointestinal bleeding
Hepatobiliary disorders	Ascites, hyperbilirubinemia/-uria, jaundice, skleral jaundice, pruritus, cholezystolithiasis
Loss of efficiency	fatigue, weariness, exhaustion, absent-mindeness, dyspnoea
Mucucutaneous disorders	alteration of the mucous membrane, xerostomia, burning sensation in mouth, tongue, or lips, epistaxis,Herpes labialis, stomatitis, mukositis
Musculoskeletal disorders	arthralgia, myalgia, musculoskeletal discomfort, seizures
Nervous system disorders	cephalea, dizziness, dysgeusia, paresthesia
Psychiatric disorders	adynamia, depression, burn-out, aggressiveness, nervousness, suicidal tendency, emotional lability, sleeping disorders, hyperventilation syndrome
Renal and urinary disorders	Urinary tract infection, pain during urination, hematuria, impotence
Respiratory disorders	sore throat, flu-like symptoms, rhinitis, cough, respiratory discomfort, bronchitis, pneumonia, parotitis, angina tonsillaris
Skin and subcutaneous tissue disorders	Angular cheilitis, eczema, erythema, rash, dermatitis, skin lesion, xerodermia, psoriasis, photosensitivity, perianal discomfort, hemorrhoid, thrombophlebitis
Skin appendage disorders	Allopezia, nail disoders
Teeth and periodontium disorders	teeth problems, gingivits, gum bleeding
Temperature regulation disorders	fever, heat intolerance, chill, sweating

3 Results

This chapter opens with **Treatment algorithm** (➪ page 31), where current guideline recommendations are deduced into flow-chart-algorithms.

Furthermore, in **Subjects** (➪ page 31) a description of demographic data, HCV-genotype, host IL-28 genotype, route of infection, pretreatment hepatic damage, and pre-treatment viral load is given.

In **Treatment monitoring** (➪ page 36) the progress of antiviral treatment, scheduled clinical contact, monitoring of treatment efficacy, and monitoring of treatment safety are reported.

Consecutively **Reported adverse events** (➪ page 42) summarizes the results of type of adverse events, as well as their particular onset and incidence during antiviral therapy.

Appearence of **Laboratory changes** (➪ page 47) is summarized briefly.

Within **Infections and infestations** (➪ page 52) the incidence of clinically relevant infections and infestations within dual- and triple-therapy regimes are investigated.

However, **Discontinuation of antiviral therapy** (➪ page 55) reports the reason and timepoint of treatment discontinuation.

Eventually, **End of treatment and follow up** (➪ page 57) delineates with SVR-rates with respect to HCV-genotype, therapy regimen, gender, viral-load, and treatment duration.

3.1 Treatment algorithm

Treatment algorithms are deduced from current guidelines.

Treatment algorithm

On basis of current guidelines and avaliable literature[22,24,32,36,46–51] treatment algorithms for dual-therapy regimes were deduced. For lack of space these algorithm-charts are attached in the Appendix to this thesis (see Section 6.1, Figure 6.1) and triple-therapy regimes (see Appendix, Section 6.1, Figure 6.2 and Figure 6.3 for BOC-based-algorithm and TVR-based-algorithm, respectively).

3.2 Subjects

A detailed description of demographic data, HCV-genotype, host IL-28 genotype, route of infection, pretreatment hepatic damage, and pre-treatment viral load is given.

During the survey period a total of 108 patients (47 receiving dual-therapy, 61 receiving triple-therapy) have been included. Demographic data with respect to the therapy regimen is given in Table 3.1. According to age and body weight, dual- and triple-therapy subgroups showed no significant difference ($p < 0.05$, exact Wilcoxon rank sum test).

Table 3.1: Demographic data of subjects prior to antiviral therapy. Data was collected during the screening appointment and at baseline.

Therapy regime	N	age [yrs] $\mu \pm \sigma$	weight [kg] $\mu \pm \sigma$	therapy-naïve	HCV-genotype 1
Dual-therapy	47	43.8 ± 13.1	43.8 ± 16.1	32 (68.1%)	23 (48.9%)
Peg-IFN-α2a + RBV	39	43.8 ± 12.8	63.7 ± 16.3	30 (76.9%)	19 (48.7%)
Peg-IFN-α2b + RBV	3	41.0 ± 20.6	70.0 ± 22.6	2 (66.7%)	2 (66.7%)
Legalon[a] + peg-IFN-α2a + RBV	5	45.3 ± 13.2	80.4 ± 9.3	0	2 (40.0%)
Triple-therapy	61	52.6 ± 9.6	52.6 ± 15.6	29 (47.5%)	61 (100%)
Peg-IFN-α2a + RBV + BOC	31	48.9 ± 9.8	75.8 ± 15.1	16 (51.6%)	30 (100%)
Peg-IFN-α2b + RBV + BOC	4	49.8 ± 6.5	71.8 ± 15.6	2 (50%)	4 (100%)
Peg-IFN-α2a + RBV + TVR	26	57.5 ± 7.4	73.4 ± 16.4	12 (46.2%)	27 (100%)

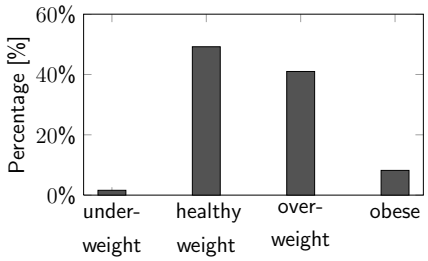
μ, arithmetic mean; σ, standard deviation; [a] Legalon-lead in.

However, the fraction of therapy-naïve patients within the tripe-therapy regimen was lower (68.1% in dual-therapy vs. 47.5% in triple-therapy). The asymmetrical distribution of HCV-genotype 1 patients yields from the fact that triple-therapy based on BOC or TVR is admitted only to genotype 1, while dual-therapy can be applied to patients bearing any HCV-genotype.

Body weight

According to the world health organization a sub-classification using the body mass index can be applied[64] (see Figure 3.1). Average body mass index prior to antiviral therapy was $(25.6 \pm 4.2)\,\mathrm{kg/m^2}$, with 1.6% underweight (BMI $< 18.5\,\mathrm{kg/m^2}$), 49.2% healthy weight (BMI $> 18.5\,\mathrm{kg/m^2}$ and $< 25\,\mathrm{kg/m^2}$), 41.0% overweight (BMI $> 25\,\mathrm{kg/m^2}$ and $< 30\,\mathrm{kg/m^2}$), and 8.2% obese (BMI $>30\,\mathrm{kg/m^2}$ and $< 35\,\mathrm{kg/m^2}$) subjects.

Fig. 3.1: BL body weight



Genotype

HCV-genotype was determined in all 108 patients, with the highest incidence of genotype 1 (77.8%, n = 84), followed by genotypes 3 (14.2%, n = 16), 2, and 4 (both 3.7%, n = 4, compare Figure 3.2). A geno-subtype classification was determineable in 88.9% of patients, with the majority being infected with HCV-geno(sub)types 1B (48.5%), 1A (27.8%) and 3A (15.5%).

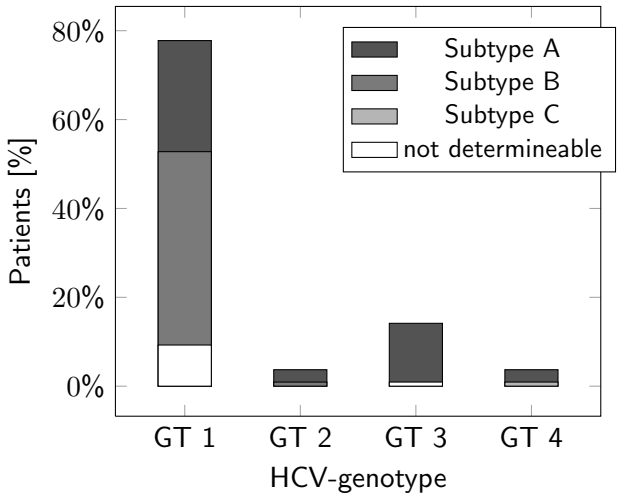
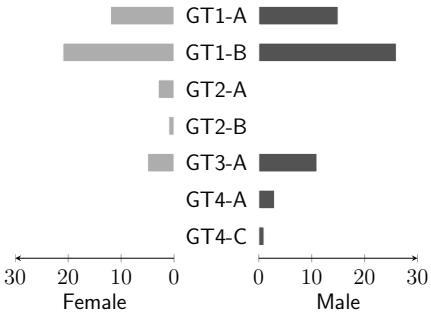


Figure 3.2: Distribution of genotype and subtype in patients which have received antiviral therapy. Subtypes are ■ A, ■ B, ■ C, and □ no subtype determineable or documented.

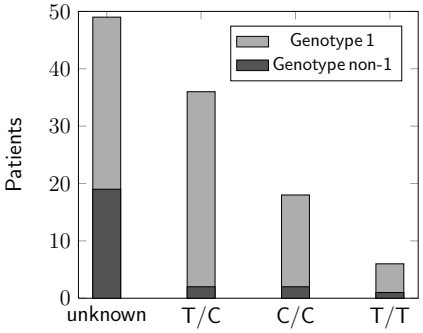
Fig. 3.3: Gender vs. genotype



Gender

46 female and 62 male patients were included. A gender difference for the most prominent HCV-genotypes 1 and 3 is not clearly given ($p = 0.12$, Fisher's exact test, two-sided. Compare Table 3.3). Surprisingly genotypes 2 and 4 exclusively appeared in female and male subjects, respectively. However, due to the limited number of patients in this subgroups (4 patients with HCV-genotype 2 and 4 patients with genotype 4) these incidence may rather be a sample size effect.

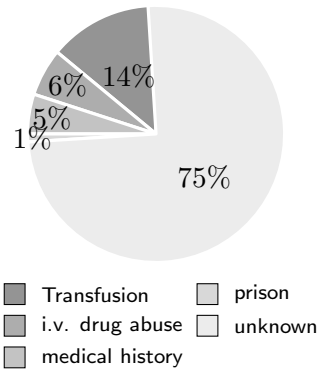
Fig. 3.4: Host IL-28 genotype



IL-28 genotype

The host IL-28 genotype was determined in 60 out of 108 patients (see Figure 3.4). In 55 (64.7%), 3 (75.0%), 1 (6.3%), and 1 (25.0%) of cases patients were bearing HCV-genotype 1, 2, 3, and 4, respectively. Host allel-types T/C, C/C, and T/T were found in 36, 18, and 6 patients, respectively. Knowledge of the host's IL-28 genotype is not imperative for any antiviral therapy, but may provide some clues about the expected treatment success. However, an IL-28 determination in commonly performed in patients bearing HCV-genotype 1.

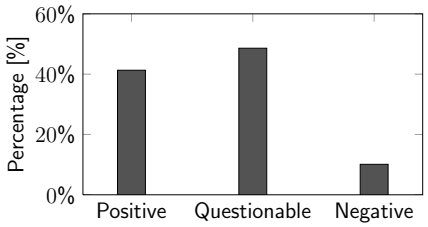
Fig. 3.5: Route of infection



Route of Infection

In 27 cases the cause of HCV-infection is assumed to be known (see Figure 3.5). Transfusion of blood products and i.v. drug abuse are most frequent (15 and 6 cases, respectively). The other assumed routes of infection are medical interventions other than transfusion of blood products (5 cases, all in foreign countries) and a prison-stay (1 case). The predominance of genotype 3 in male subjects (11 vs. 5) may relate to both, a more frequent appearance of genotype 3 in i.v. drug abusing subjects and the fact that there are more male than female drug abusers (compare Figure 3.3). However, 5 of 6 subjects where i.v. drug abuse is the suspected route of HCV-infection are male. A predominance of genotype 1 is indicated within patients with blood product transfusion history (11 GT 1 vs. 4 non-GT 1, compare also Pawlotsky et al. 1995[65]).

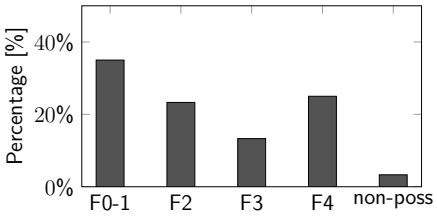
Fig. 3.6: Substance abuse



Substance abuse

In 45 patients a former and/or ongoing substance abuse was documented (see Figure 3.6). This includes repetitive consumption of alcohol, drugs, and/or nicotine. Substance abuse was excluded in 11 subjects, with the remaining 53 leaving questionable former or ongoing substance abuse (primarily alcohol and/or nicotine consumption).

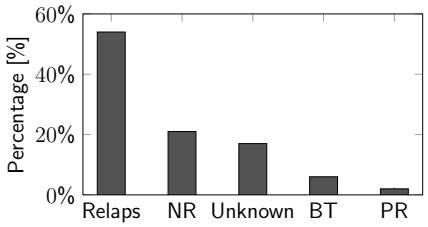
Fig. 3.7: Fibrosis grading



Fibrosis grading

Fibrosis /cirrhosis grading was performed before treatment either due to liver biopsy and histological grading or non-invasive using transient elastography (FibroScan®). Participating subjects had absent or mild fibrosis (Metavir F0/F1, Fibroscan $< 7.0\,\text{kPa}$), significant fibrosis (F2, $< 9.0\,\text{kPa}$), severe fibrosis (F3, $< 12.5\,\text{kPa}$), and cirrhosis (F4, $> 12.5\,\text{kPa}$) in 35.0%, 23.3%, 13.3%, and 25.0%, respectively (see Figure 3.7). In the remaining 3.3% of subjects an exact grading was not possible. However, FibroScan is capable of determining fibrosis from cirrhosis, but a valid subclassification of fibrosis grade has been shown to be inaccurate[66].

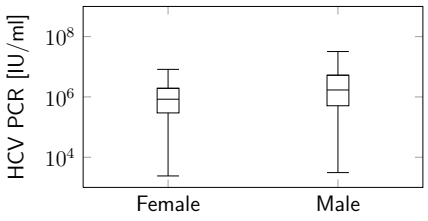
Fig. 3.8: Pre-Treatment



Pre-treatment

A total of 47 patients were treatment experienced (i.e. 44.0% patients with former peg-IFN-α/RBV dual-therapy, or peg-IFN-α mono-therapy). Those are distributed over dual- (15 patients) and triple-therapy 32 patients. Results of previous therapy were either viral relaps (26 patients), unknown (7 patients), viral partial-response (PR, 1 patient), viral non-response (NR, 10 patients), or viral breakthrough (BT, 3 patients, see Figure 3.8).

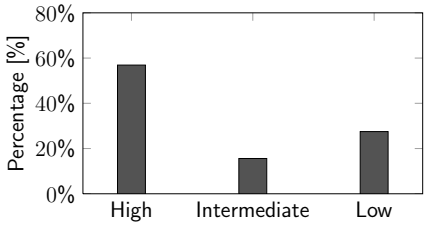
Fig. 3.9: Baseline HCV-RNA



Viral load

The median HCV-RNA at baseline (defined as closest HCV-RNA before any antiviral treatment was started) was 1 200 000 IU/ml (lower and upper quartile are 372 000 IU/ml and 3 400 000 IU/ml, respectively). A significant difference between viral load in female and male subjects was found ($p < 0.003$, student's unpaired t-test, two-sided, see Figure 3.9).

Fig. 3.10: Baseline HCV-RNA



High viral load (HCV-RNA $\geq 800\,000$ IU/ml), intermediate viral load (HCV-RNA $< 800\,000$ IU/ml and $\geq 400\,000$ IU/ml), and low viral load (HCV-RNA $< 400\,000$ IU/ml) was found in 56.9%, 15.6%, and 27.5%, respectively (see Figure 3.10).

Furthermore, known risk factors to antiviral treatment success have been found in a few cases:

- A resolved co-infection was found in 13 patients (10 cases of *Hepatitis A Virus* (HAV) and/or HBV, 3 cases of tuberculosis, and 1 case of borreliosis).
- Diabetes mellitus type 2 (insulin depended) was found in 6 patients.
- Chronic kidney disease was found in 2 patients (one of them with the need of dialysis).
- Positive family history of HCV was found in 2 patients.

Contrary, an immunization against HAV and/or HBV was done by 12 patients. However, no current immune modulating therapy was found in the study population.

3.3 Treatment monitoring

The progress of antiviral treatment, scheduled clinical contect, monitoring of treatment efficacy, and monitoring of treatment safety are summarized.

3.3.1 Clinical contact

Clinical contact

In this thesis more than 1 375 clinical contacts to the patients were carried together including clinical records, patients history, laboratory and molecular data, and–if available–information acquired during other clinical trials. Data was acquired from both handwritten and/or printed as well as electronic health records.

The date of each clinical contact included in this thesis with respect to the particular therapy baseline is given in Figure 3.11.

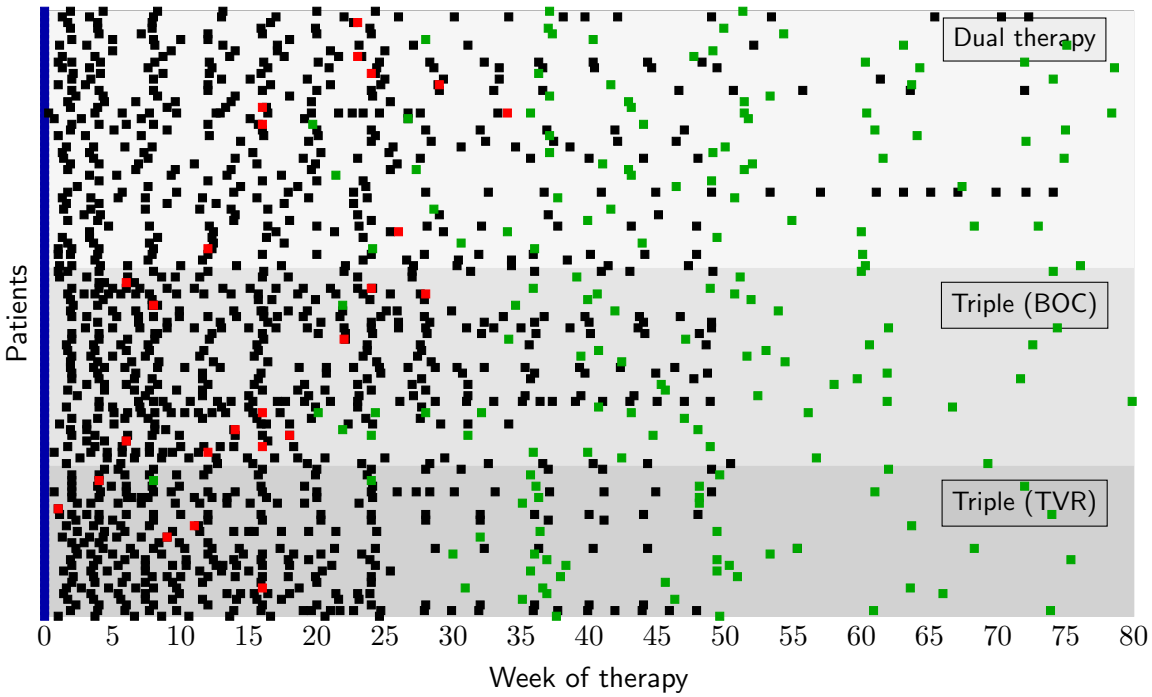


Figure 3.11: Date of clinical contact during antiviral therapy. Rows represent patients with dual- or triple-therapy (discriminable by background color). Squared marks indicate the week of clinical contact to the patient: ■ start of therapy (in particular baseline, week 0), ■ ongoing therapy, ■ treatment discontinuation, ■ end of treatment and follow up. There is no designed order within the therapy regimes since patients are included in sequence of the availability of their health record (compare Section 3.2). Triple (BOC) and Triple (TVR) are Boceprevir- and Telaprevir-based triple-therapy regimes, respectively.

As recommendations state clinical contacts to the patient have been predominately scheduled in weeks 2, 4, 8, 12, and 24 (compare Table 1.7). This can be suggestively been seen as the date of clinical contact shown in Figure 3.11 more or less confluences into vertical lines at the implied weeks 2, 4, 8, 12, and 24.

The number of patients who appear at their appointment during therapy as well as the number of patients with ongoing therapy, end of treatment, and treatment discontinuation is given in Figure 3.12. The discrepancy between the number of patients who actually appear at the appointment and those under ongoing therapy did not result from bad compliance alone. The difference results primarily from a dynamic scheduling with the patient. However, the highest fraction of patients actually appearing at the appointment was given at baseline, and at weeks 3–5, 10–14, 22–26, and 26–30.

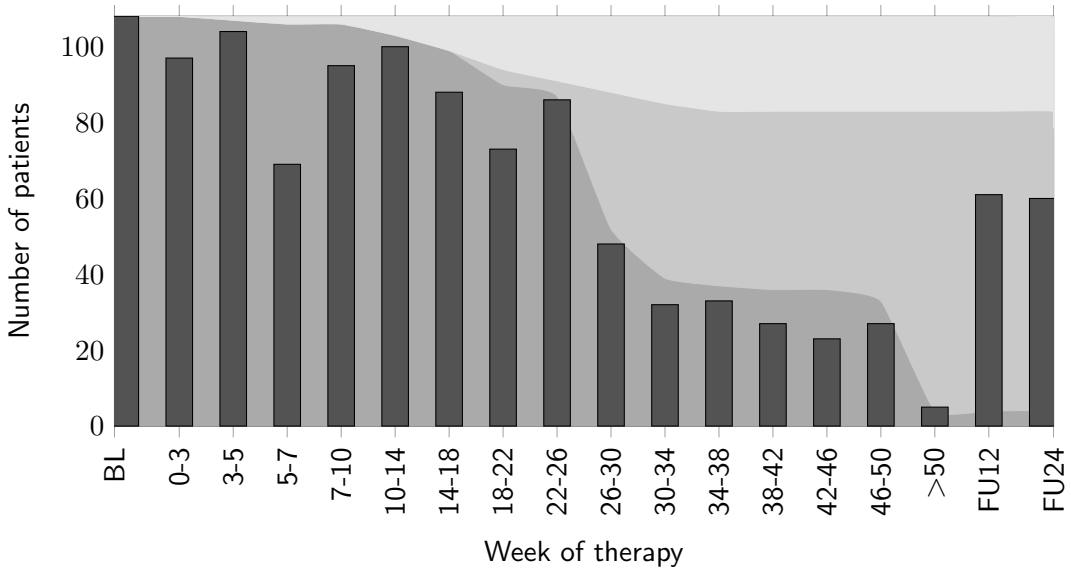


Figure 3.12: Black bars indicate the number of patients who appear to an appointment during therapy. Background color indicates number of patients with ■ ongoing treatment, ■ end of treatment achieved, and ■ treatment discontinuation. BL, baseline; FU12 and FU24, follow up at weeks 12 and 24 post end of treatment, respectively.

3.3.2 Monitoring of treatment efficacy

Treatment efficacy

Monitoring of treatment efficacy was done by repetitive measurements of HCV-RNA during antiviral treatment (see Figure 3.13). This was done at least in the recommended time slots (compare to Table 1.7) but additional measurements have been done during the entire antiviral therapy and follow up.

Treatment response is subclassified due to the magnitude of decay in HCV-PCR into RVR, *Early Virological Response* (EVR), and *Delayed Virological Response* (DVR) for dual-therapy and ER, LR, and *Extended Rapid Virological Response* (eRVR) for triple-therapy (see also definitions in Glossary).

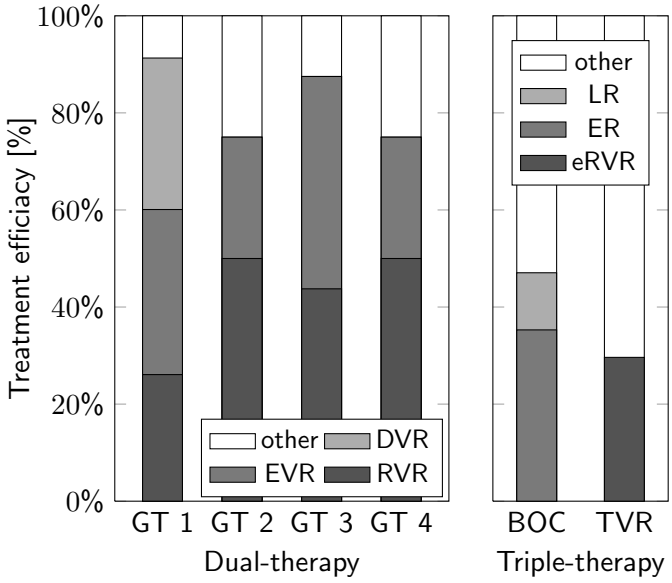


Figure 3.13: Treatment efficacy according to the virological response to antiviral therapy is shown. ■ RVR, rapid virological response, ■ EVR, early virological response, ■ DVR, delayed virological response, ■ ER, early response, ■ LR, late response, ■ eRVR extended rapid virological response, □ other, HCV-PCR was not quantified, the patient did not appear at the clinic, or the patient's treatment has already been stopped. GT, HCV-genotype; BOC, Boceprevir-based triple-therapy; TVR, Telaprevir-based triple-therapy.

Altogether viral response to antiviral treatment lead to a more rapid response in HCV-RNA decline with TVR-triple-therapy compared to dual-therapy or BOC-triple-therapy (see Figure 3.14). The latter results from the fact that BOC-guided triple-therapy uses a 4-weeks lead-in with peg-IFN-α + RBV. The delayed viral response with BOC-triple-therapy may be due to the more therapy experienced patients within this subgroup.

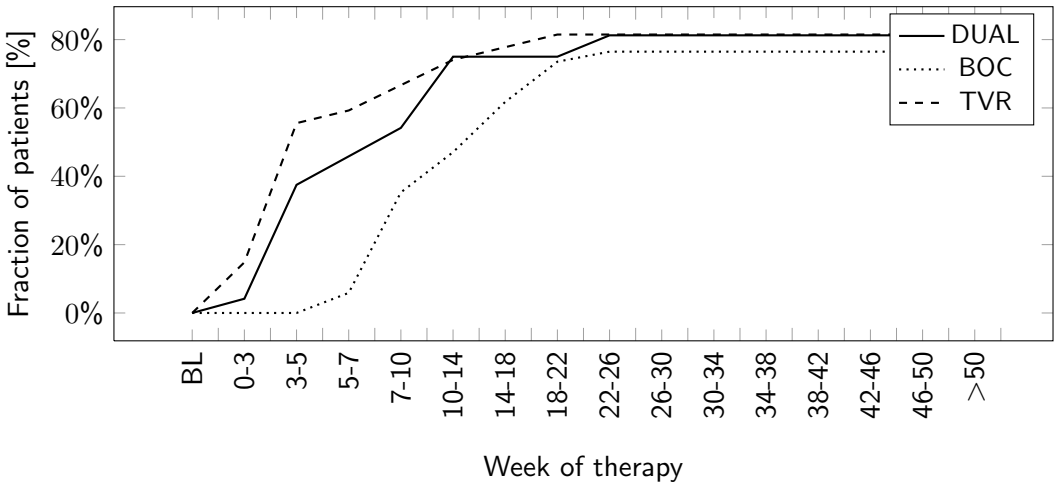


Figure 3.14: Fraction of patients with documented viral eradication, i.e. undetectable HCV-RNA in a sensitive assay. BL, baseline; DUAL, dual-therapy; BOC, Bocepreir-based triple-therapy; TVR, Telaprevir-based triple-therapy.

3.3.3 Monitoring of treatment safety

Treatment safety

To assure treatment safety patients were asked to appear at the outpatient clinic in 2 – 4 weeks intervals. In rare cases the scheduled appointment was failed, thus the patient's adverse events (if any) were questioned by phone and documented in the patients health record. By doing so, the incidence of adverse events and especially infections and infestations during antiviral therapy was assessed. Figure 3.15 shows the number and fraction of patients reporting of adverse events for each time slot during antiviral therapy and follow up.

The average fraction of patients reporting adverse events is $(67 \pm 18)\%$, $(71 \pm 26)\%$, and $(74 \pm 24)\%$ in dual-therapy, BOC-, and TVR-based triple-therapy, respectively (see Figure 3.16). Although there were numerically less adverse events reported from patients with dual-therapy, there was no significant difference found (student's paired t-test, two-sided, 95% confidence interval).

The average number of adverse events per patient and adverse events per week are given in Figure 3.17 and Figure 3.18, respectively. A significant difference between the number of reported adverse events was found for weeks 7 – 10, 10 – 14, 22 – 26, and follow up 24 weeks post end of treatment ($p<0.05$, student's unpaired t-test, one-sided, 95% confidence interval).

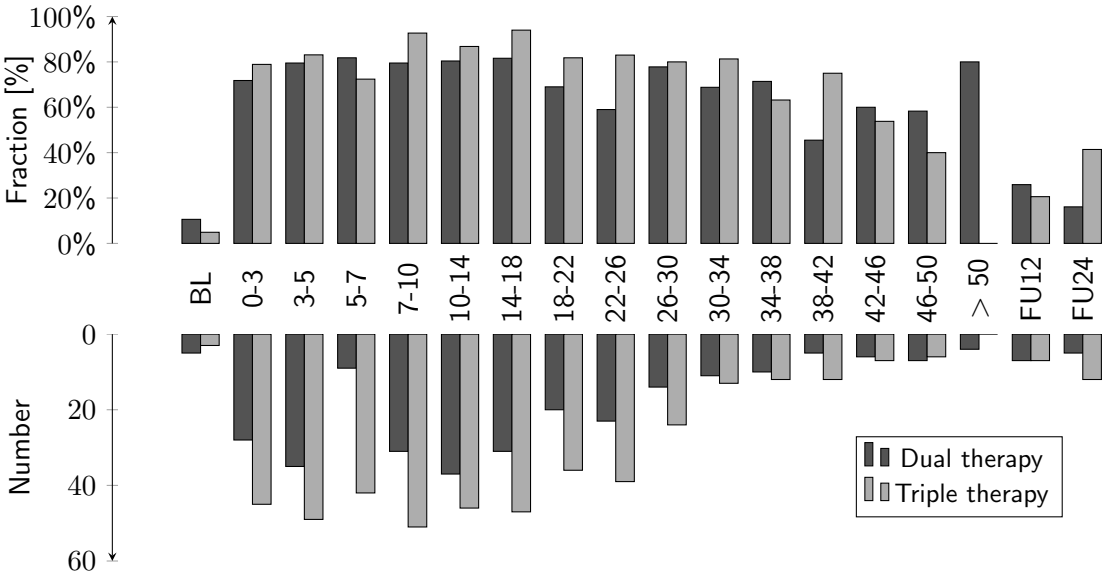


Figure 3.15: Number (at bottom) and fraction (at top) of patients reporting of adverse events during respective time slots for ■ dual and ■ triple-therapy. With progression in therapy duration the number of patients who have already reached their end of treatment increases, thus the number of patients with ongoing treatment decreases. The latter may lead to an overvaluation of the fraction-of-patients values (at top) post week 26–30. Especially weeks > 50 may be interpreted with caution since there were very few patients under ongoing therapy left.

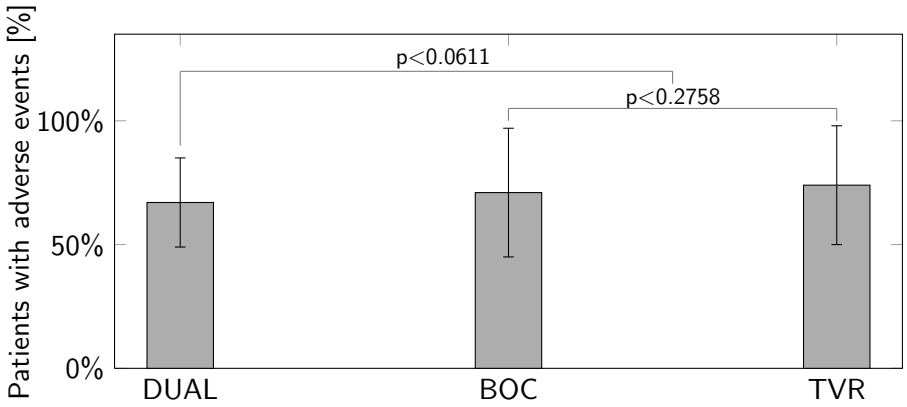


Figure 3.16: Average fraction ± standard deviation of patients with adverse events during therapy. No significant difference between dual- and triple-therapy regimes was found (student's paired t-test, one-sided, 95% confidence interval). DUAL, dual-therapy, BOC, Boceprevir-guided triple-therapy, TVR, Telaprevir-guided triple-therapy.

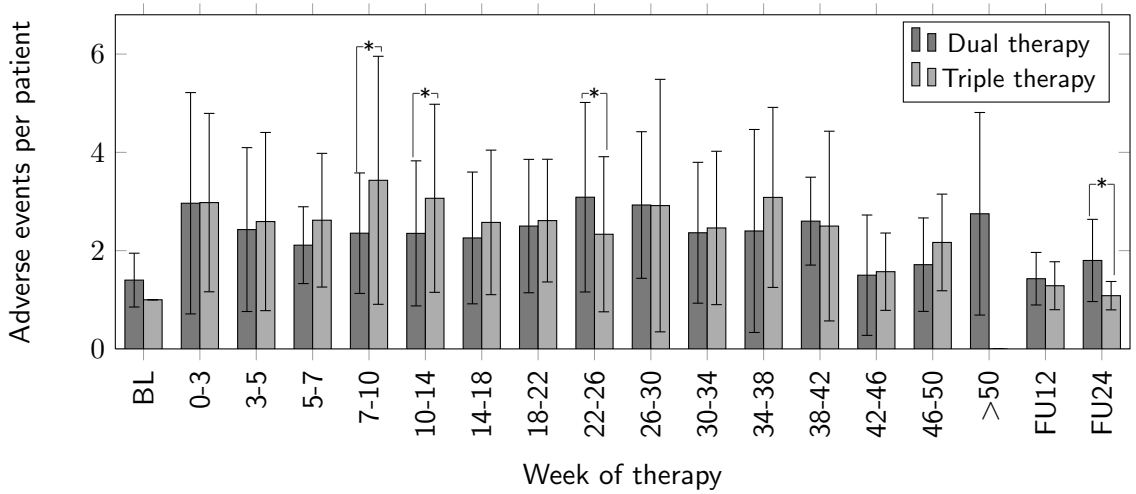


Figure 3.17: Average number ± standard deviation of adverse events per patient. The asterisk indicates a significant difference was found for weeks 7–10, 10–14, 22-26, and follow up 24 weeks post end of treatment ($p < 0.05$, student's unpaired t-test, one-sided, 95% confidence interval).

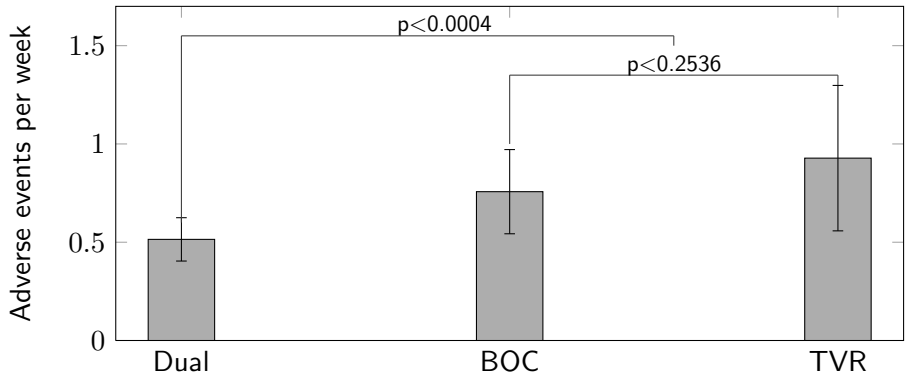


Figure 3.18: Average number ± standard deviation of adverse events per week of antiviral therapy. A significant difference was found between dual- and triple-therapy. DUAL, dual-therapy, BOC, Boceprevir-guided triple-therapy, TVR, Telaprevir-guided triple-therapy.

The average adverse events per week of antiviral therapy were 0.5 ± 0.1, 0.8 ± 0.2, and 0.9 ± 0.4 for dual-therapy, BOC-based triple-therapy, and TVR-based triple-therapy, respectively. A significant difference between the average number of adverse events per week of antiviral therapy was found between dual- and all triple-therapy patients ($p < 0.0004$, student's paired t-test, two-sided, 95% confidence interval). No significance was found between both triple regimes (BOC vs. TVR, $p < 0.2535$, student's paired t-test, two-sided, 95% confidence interval).

3.4 Reported adverse events

This section summarizes the type of adverse events, as well as their particular onset and incidence during antiviral therapy.

This section summarizes the results regarding adverse events reported during antiviral therapy. A detailed list of all used terms when adverse events were documented is given in Appendix 6.3. Adverse events with an overall occurrence of more than 1% (i.e. the adverse event is reported by more than 1 patient) are given alongside with their particular incidence in Table 3.2, 3.3, and 3.4. Adverse events reported by not more than 1 patient are given in Table 3.5. Figure 3.19 shows the frequency of adverse events reported by more than 10% of patients with respect to their week of appearance.

Table 3.2: Incidence of adverse events with an overall occurrence of more than 1% (i.e. the adverse event is reported by more than 1 patient). Organ system categories are modified from CTCAE[63].

Adverse event	**Dual therapy** *N = 47*	Peg-IFN-α-2a + RBV *N = 39*	Peg-IFN-α-2b + RBV *N = 3*	Legalon + Peg-IFN-α-2a + RBV, *N = 5*	**Triple therapy** *N = 61*	Peg-IFN-α-2a + RBV + BOC, *N = 31*	Peg-IFN-α-2b + RBV + BOC, *N = 4*	Peg-IFN-α-2a + RBV + TVR, *N = 26*
Blood and lymphatic system disorders *								
Anemia	44	38	2	4	57	30	3	24
Leukopenia	46	39	3	4	56	28	4	24
Thrombopenia	32	28	2	2	46	23	3	20
Lymphopenia	31	27	1	3	45	23	4	18
Neutropenia	39	32	2	4	53	29	3	21
Cardiac disorders and vascular disorders								
Hypertension	1	1			2	1		1
Hypotension, circulatory weakness	4	4			6	3	1	2
Cardial disorders^{NOS}					2	1		1
Ear disorders								
Otitis, Otomycosis	1		1		2	1		1
Ear disorders^{NOS}	5	3		2	6	1	1	4
Eye disorders								
Burning eye, dry eye	3	2	1		9	3		6
Acute disturbance of vision	5	5			3	2		1

^{NOS} not otherwise specified.

* for a detailed description of blood disorders see Section 3.5.

Table 3.3: Incidence of adverse events, continued from Table 3.2.

Adverse event	**Dual therapy** *N = 47*	Peg-IFN-α-2a + RBV *N = 39*	Peg-IFN-α-2b + RBV *N = 3*	Legalon + Peg-IFN-α-2a + RBV, *N = 5*	**Triple therapy** *N = 61*	Peg-IFN-α-2a + RBV + BOC, *N = 31*	Peg-IFN-α-2b + RBV + BOC, *N = 4*	Peg-IFN-α-2a + RBV + TVR, *N = 26*
Fluid shift disorders								
Peripheral edema, swelling					4	4		
Gastrointestinal disorders								
Diarrhoe	2	1		1	24	16	2	6
Nausea and vomiting	16	14		2	20	9		11
Loss of appetite	12	10		2	11	5		6
Abdominal pain	7	4		3	10	6		4
Dyspepsia	1	1			6	4		2
Gastroenteritis					3	2	1	
Intestinal disorders^{NOS}	2	2			5	2	1	2
Hepatobiliary disorders								
Jaundice	3	1		2	2			2
Pruritus	14	12	1	1	28	11	2	15
Loss of efficiency								
Fatigue	34	29	1	4	52	27	4	21
Asthenia	10	10			11	8		3
Impaird concentration	3	3			3	2	1	
Dyspnoe	7	7			20	11	2	7
Mucucutaneous disorders								
Mucucutaneous alteration^{NOS}	5	3		2	10	6	2	2
Burning sensation orally	4	4			1	1		
Stomatitis, mucositis	3	3			1	1		
Xerostomia	2	2			13	6	1	6
Herpes labialis	2	2			4	3		1
Epistaxis	3	3			8	4	1	3
Musculoskeletal disorders								
Arthralgia	11	11			10	6	2	2
Myalgia	8	6	1	1	13	7	1	5
Seizures					6	1	1	4
Musculoskeletal discomfort^{NOS}	6	5		1	11	6	1	4
Nervous system disorders								
Cephalea	14				21	9	2	10
Dizziness	11	10		1	16	10	1	5
Dysgeusia	2	2			16	10	2	4
Parestesia, dysesthesia	2	2			5	2		3
Psychiatric disorders								
Adynamia	2	1		1	2	2		
Depression	8	8						
Aggressiveness	9	8	1		6	4		2

^{NOS} not otherwise specified.

Table 3.4: Incidence of adverse events, continued from Table 3.3.

Adverse event	**Dual therapy** *N = 47*	Peg-IFN-α-2a + RBV *N = 39*	Peg-IFN-α-2b + RBV *N = 3*	Legalon + Peg-IFN-α-2a + RBV, *N = 5*	**Triple therapy** *N = 61*	Peg-IFN-α-2a + RBV + BOC, *N = 31*	Peg-IFN-α-2b + RBV + BOC, *N = 4*	Peg-IFN-α-2a + RBV + TVR, *N = 26*
Psychiatric disorders continued								
Nervousness	4	3		1	2	2		
Suicidal tendency	1	1			1	1		
Emotional lability	12	11		1	8	2	2	4
Sleeping disorders	9	7	1	1	13	8	1	4
Renal and urinary disorders								
Urinary tract infection	2	2			4	1	1	2
Urogenital disorders^{NOS}	1	1			10	4	1	5
Respiratory disorders								
Sore throat	2	2			5	2	1	2
Flu-like symptoms	16	13	2	1	9	7	2	
Angina tonsillaris					3	3		
Rhinitis					3	2		1
Coughing	6	4		2	15	7	1	7
Bronchitis, Pneumonia	3	2		1	1			1
Respiratory discomfort^{NOS}	3	3			2	2		
Skin and subcutaneous tissue disorders								
Angular cheilitis	4	3		1	5	1		4
Rash, eczema, erythema	14	13		1	30	12	2	16
Dermatitis	1			1	3	2		1
Injection site reaction	3	3			2			2
Xerodermia	20	17	1	2	20	9		11
Skin lesion^{NOS}	5	5			10	5		5
Psoriasis	1	1			4	1		3
Photosensitivity	1	1			5	2		3
Perianal discomfort	1	1			6	1		5
Thrombophlebitis	2	1		1	1			1
Skin appendage disorders								
Alopezia	8	7		1	14	7	1	6
Teeth and periodontium disorders								
Gingivitis, gum bleeding	3	3			7	5		2
Temperature regulation disorders								
Fever	13	11	1	1	21	9	3	9
Chills	8	7	1		10	5	2	3
Sweating, heat intolerance	11	11			5	4	1	

^{NOS} not otherwise specified.

Table 3.5: Adverse events reported by not more than 1 patient.

therapy-regimen / adverse event
Peg-IFN-α-2a + RBV
☐ Lymphadenopathy, splenomegaly, cholecystolithiasis
Peg-IFN-α-2b + RBV
Legalon + Peg-IFN-α-2a + RBV
Peg-IFN-α-2a + RBV + BOC
☐ Nycturia, pleural effusion, exacerbation of immune thyreopathy, ascites
Peg-IFN-α-2b + RBV + BOC
☐ Acute cacosmia
Peg-IFN-α-2a + RBV + TVR
☐ Parotitis, hyperventilation, hemorrhoids, proctitis, colitis, gastrointestinal bleeding, nail dystrophy, conjunctivitis, papillary bleeding, impotence, hypermenorrhea

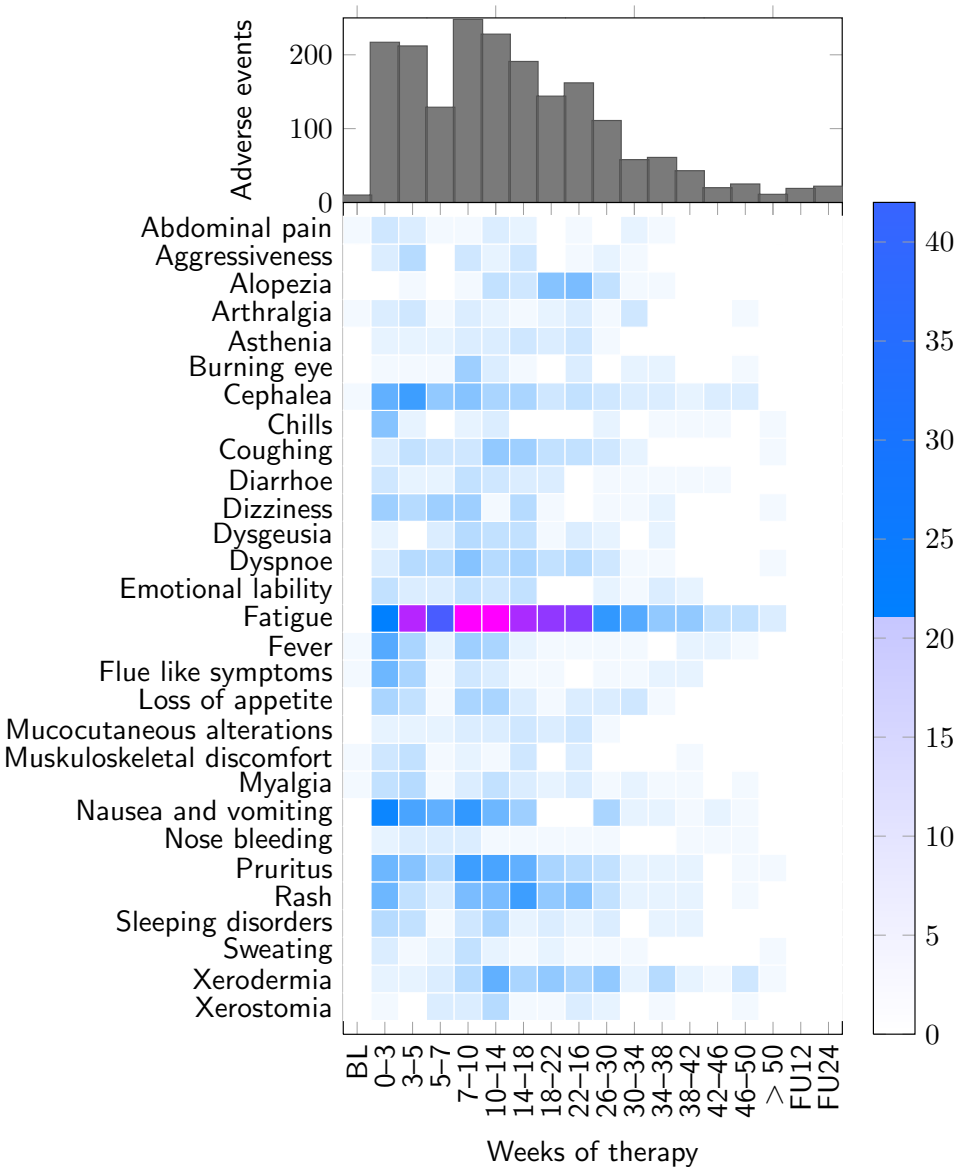


Figure 3.19: Clinical adverse events reported by more than 10% of patients during antiviral therapy. Colored mapping at the bottom shows the frequency of adverse events; the bar plot at the top gives the sum of reported adverse events. Adverse events are given in alphabetic order. BL, baseline, FU12 and FU24 are follow up at weeks 12 and 24 after end of treatment, respectively.

3.5 Laboratory changes

As part of monitoring treatment safety blood samples were drawn regularly.

Laboratory reference values apply to the Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University Graz. An overview of acronyms and reference value is given in the Appendix (Section 6.2). Differences in limits for female and male subjects are taken into account for statistical analysis, but are not shown in this section's figures separately.

Laboratory changes during antiviral treatment are summarized in Figure 3.20. Given are the frequencies of laboratory changes for reaching lower and higher levels compared to the laboratory value's lower and upper limit, respectively. In general, hematologic and hepatic values are affected most often.

Below the respective lower limit were hemoglobin (HB, 76.9%), hematocrit (HCT, 81.9%), lymphocyte-fraction (LY, 44.7%), neutrophil-fraction (NEUTRO, 63.6%), red blood count (RBC, 71.2%), platelets (PLT, 55.0%), and white blood count (WBC, 86.0%). However, above the respective upper limit were alanine aminotransferase (ALT, 25.7%), aspartate aminotransferase (AST, 44.2%), gamma glutamyl transferase (GGT, 36.5%), triglycerides (TRI, 35.1%), and uric acid (UA, 32.4%).

The progression of red blood count, white blood count, and platelet count for dual-therapy, BOC-based triple-therapy, and TVR-based triple-therapy is given in Figure 3.21. At baseline and during follow-up cell count values was within their respective limits. At the same time as antiviral treatment begins a rapid decrease of cell count was found, which was most pronounced in leukocytes. However anemia and leukopenia was found in almost all patients independent of treatment regimen. A significant difference between dual-therapy and triple-therapy was found particularly for erythrocytes count and platelet count ($p < 0.05$, student's paired t-test, two-sided, 95% confidence interval).

A similiar progression was found for neutrophil count and lymphocyte count (see Figure 3.22). However, the decrease was less distinct compared to red blood count. During antiviral treatment mean values of neutrophiles and lymphocytes were about their respective lower limit. No noteworthy significant difference between therapy regimen was found.

Number of patients suffering from severe alterations in red blood count, neutrophiles count, and platelet count together with corresponding limits are given in Table 3.6 (compare also Table 3.2).

An initial decrease of hepatic values (Alanine aminotransferase (ALT) and aspar-

tate aminotransferase (AST), and gamma-glutamyl transpeptidase (GGT)) was found in all therapy regimen. The difference between regimen in treatment weeks > 22 is primarily evoked by smaller subgroups (due to end of treatment or treatment discontinuation) and thus more imprecise statistical results. No noteworthy significant difference between therapy regimen was found.

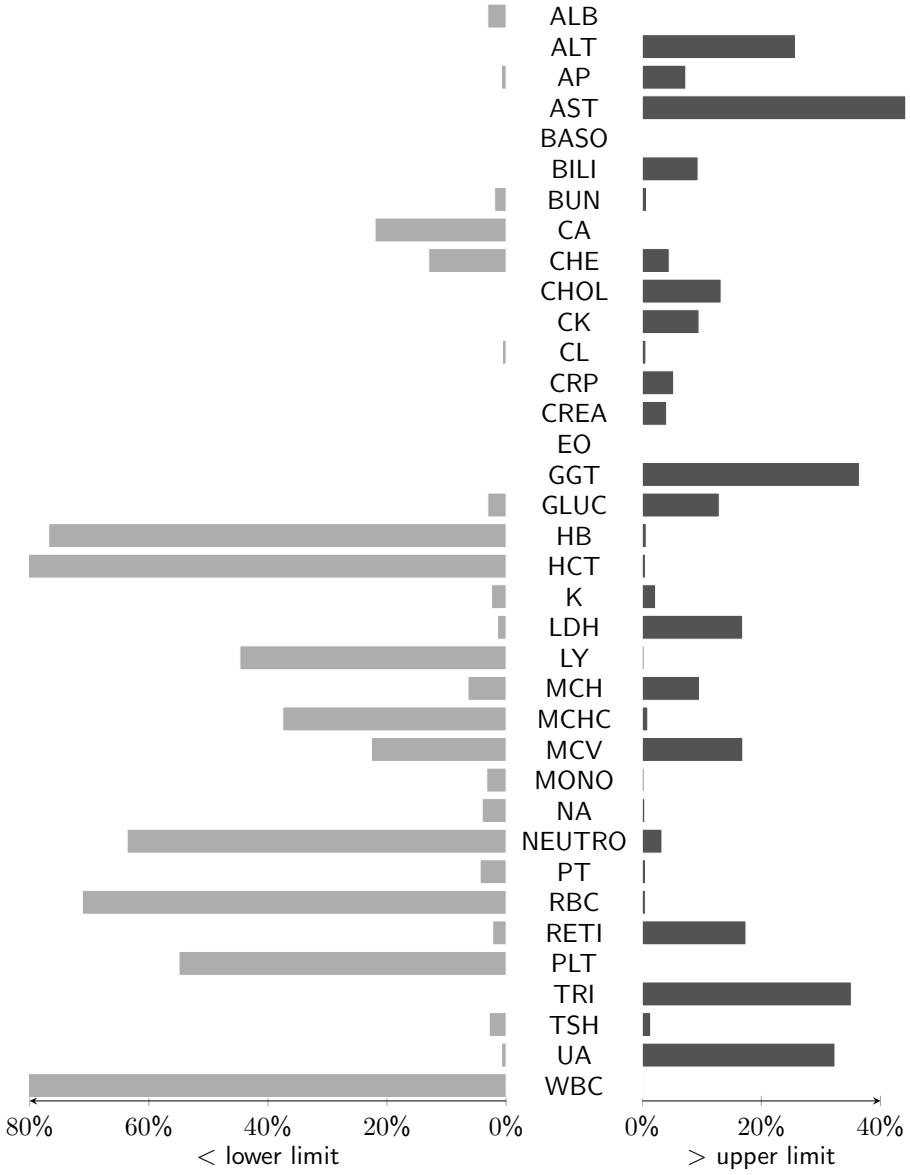


Figure 3.20: Frequency of laboratory chages during antiviral treatment. Baseline values and follow-up values are not included in this figure. ■, dropping of the laboratory value below the respective lower limit. ■, exceeding of the laboratory value above the respective upper limit. Lower and upper limits with respect to the patients gender. For a decription of acronyms and reference values see Table 6.1 in the Appendix.

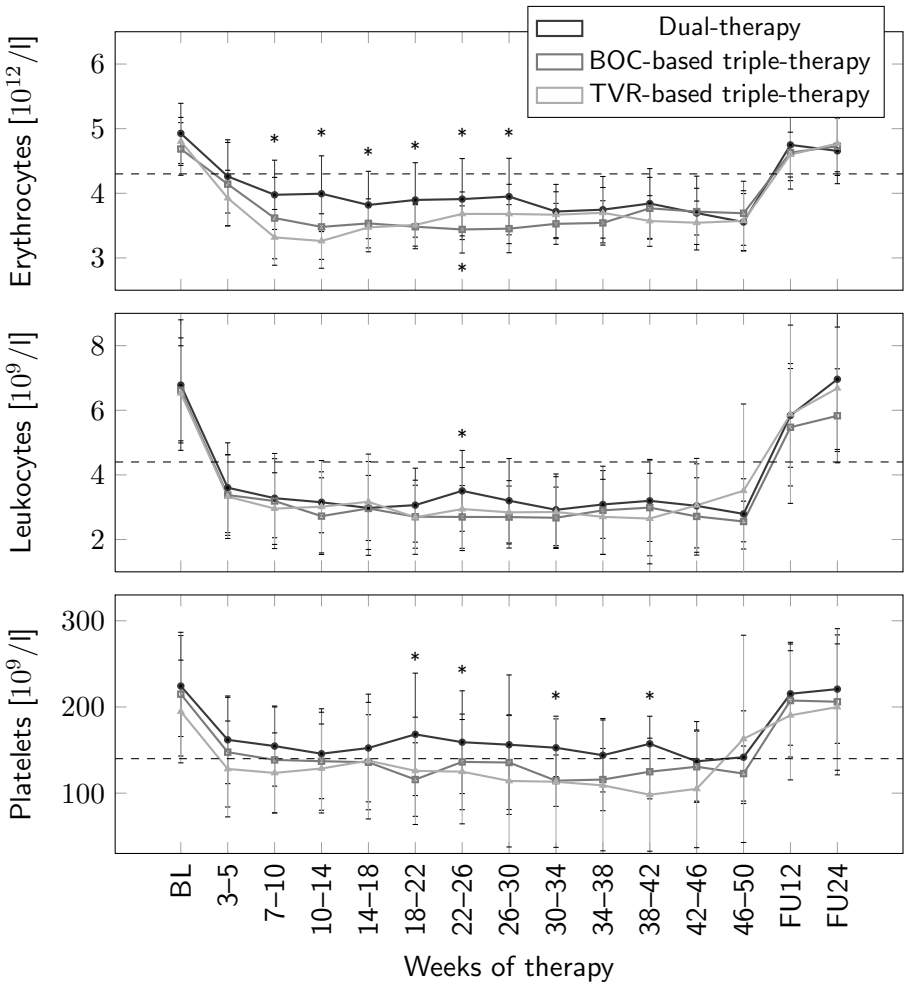


Figure 3.21: From top to bottom, serum erythrocytes, leukocytes, and platelet count during antiviral treatment are given. Dashed lines indicate the particular lower limit, i.e. erythrocytes: 4.1×10^{12}/l (female) and 4.5×10^{12}/l (male), leukocytes: 4.4×10^{9}/l, and platelets: 140×10^{9}/l. Asterisks above and below the deviation bars indicate significant difference in dual-therapy vs. triple-therapy, and BOC-based triple-therapy vs. TVR-based triple-therapy, respectively ($p < 0.05$, student's paired t-test, two-sided, 95% confidence interval). BL, baseline; FU12, follow-up 12 weeks post end of treatment; FU24, follow-up 24 weeks post end of treatment.

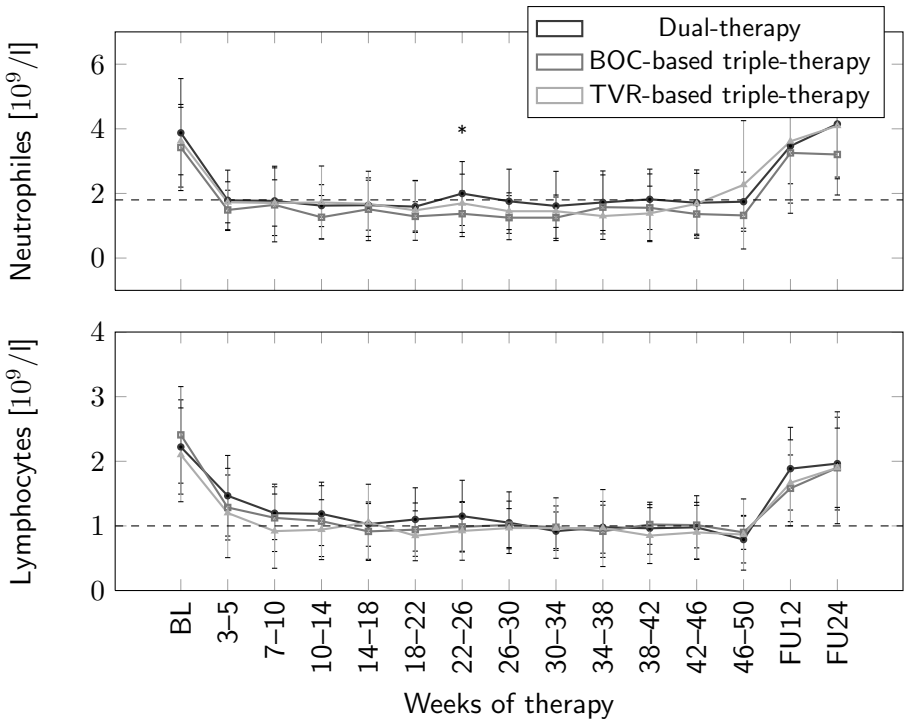


Figure 3.22: Serum neutrophiles and lymphocytes count during antiviral treatment. Dashed lines indicate the lower limit, i.e. neutrophiles: 1.8×10^9/l, and lymphocytes: 1.0×10^9/l. The asterisk indicate a significant difference in dual-therapy vs. triple-therapy in week 22 – 26 ($p < 0.05$, student's paired t-test, two-sided, 95% confidence interval). No significant difference was found for lymphocytes count. BL, baseline; FU12, follow-up 12 weeks post end of treatment; FU24, follow-up 24 weeks post end of treatment.

Table 3.6: Severe alteration of red blood count, neutrophiles count, and platelet count.

Adverse event (lower limit)	**Dual therapy** *N = 47*	Peg-IFN-α-2a + RBV *N = 39*	Peg-IFN-α-2b + RBV *N = 3*	Legalon + Peg-IFN-α-2a + RBV, *N = 5*	**Triple therapy** *N = 61*	Peg-IFN-α-2a + RBV + BOC, *N = 31*	Peg-IFN-α-2b + RBV + BOC, *N = 4*	Peg-IFN-α-2a + RBV + TVR, *N = 26*
Anemia (< 8.0 g/dl)	7	6		1	6	1	0	5
Neutropenia ($< 0.5 \times 10^9$/l)	13	12		1	16	10	1	5
Thrombopenia ($< 50 \times 10^9$/l)	8	7		1	5			5

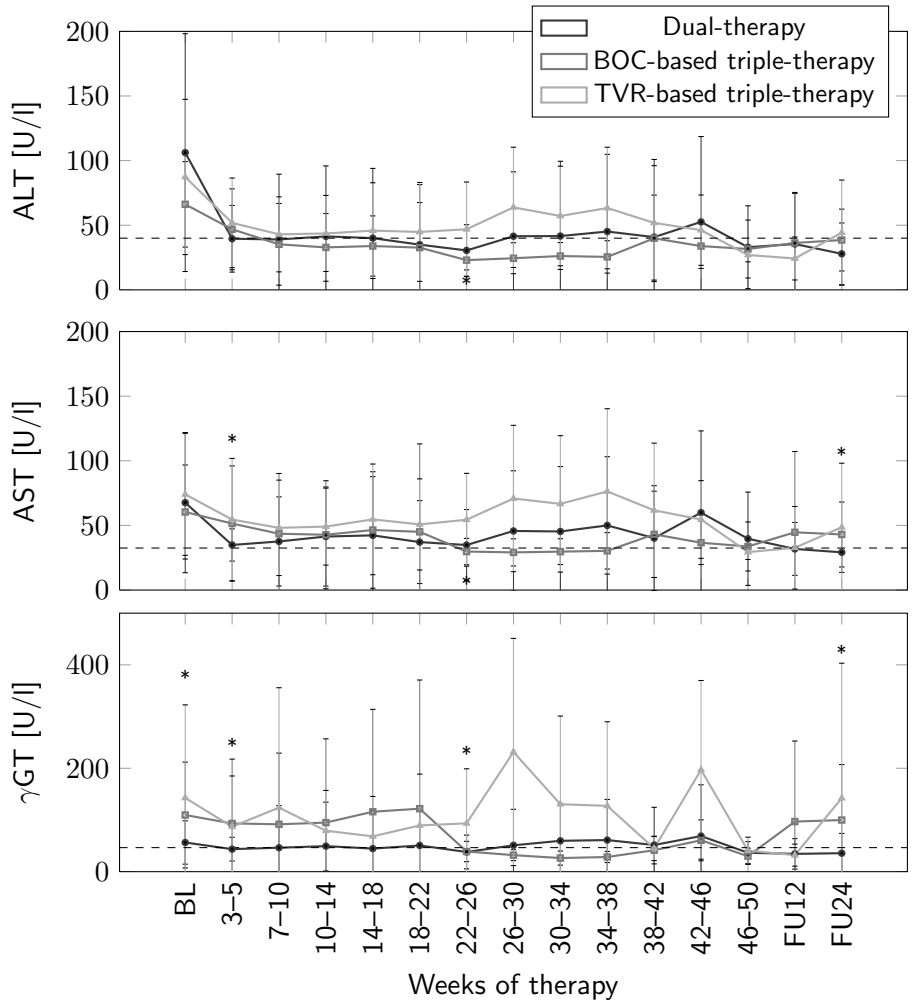


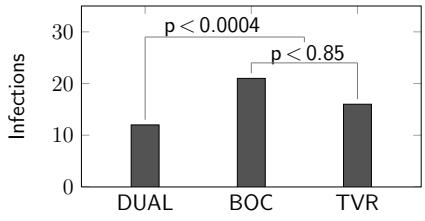
Figure 3.23: From top to bottom, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transpeptidase (γGT) during antiviral treatment. Dashed lines indicate the upper limit, i.e. AST: 30 U/l (female) and 35 U/l (male), ALT: 35 U/l (female) and 45 U/l (male), and γGT: 38 U/l (female) and 55 U/l (male). Asterisks above and below the deviation bars indicate significant difference in dual-therapy vs. triple-therapy, and BOC-based triple-therapy vs. TVR-based triple-therapy, respectively ($p < 0.05$, student's paired t-test, two-sided, 95% confidence interval). BL, baseline; FU12, follow-up 12 weeks post end of treatment; FU24, follow-up 24 weeks post end of treatment.

3.6 Infections and infestations

Consecutively the incidence of clinically relevant infections and infestations within dual- and triple-therapy regimes are reported.

A clinically relevant infection and/or infestation is given if either clinical, radiological, and/or laboratory evidence is given and anti-infective medication and/or hospitalization is necessary. However, a clinically relevant infection and/or infestation need not always to be followed by treatment discontinuation. Adverse event related discontinuation of therapy does not necessarily yield from a clinically relevant infection or infestation.

Fig. 3.24: Clinically relevant infections



Alltogether 49 clinically relevant infections and/or infestations were documented in 41 patients. Infections and/or infestations occurred 12, 21, and 16 times in 11 patients receiving dual-therapy, 16 patients receiving BOC-based triple-therapy, and 14 patients receiving TVR-based triple-therapy, respectively (see Figure 3.24). Correspondingly clinically relevant infections and/or infestations were reported by 23.4%, 47.1%, and 51.9% of patients with dual-, BOC-based triple-, and TVR-based triple-therapy. A significant difference in the incidence of clinically relevant infections and/or infestations was found between triple-therapy and dual-therapy regimen (odds ratio 4.5, 95% CI: 2.0 – 10.3, $p < 0.0004$, Fisher's exact test, two-sided) . However, the difference between BOC-based and TVR-based triple-therapy was not statistical significant (odds ratio 1.1, 95% CI: 0.4 – 3.1, $p = 1$, Fisher's exact test, two-sided).

Discontinuation

In patients with clinically relevant infections and/or infestations, therapy discontinuation was necessary in 0, 2, and 4 cases for dual-therapy, BOC-guided triple-therapy, and TVR-guided triple-therapy, respectively. No statistical difference was found between therapy regimen ($p > 0.31$, Fisher's exact test, two-sided).

A detailed list of documented clinically relevant infections and infestations together with the week of their appearance and the need for hospitalization and/or antibiotic treatment for dual-therapy, BOC-guided triple-therapy, and TVR-guided triple-therapy are given in Tables 3.7 and 3.8.

Table 3.7: Clinically relevant infections and infestations during antiviral treatment in patients receiving dual-therapy. See also Table 3.8.

therapy-regimen / week and type of infection or infestation	
Peg-IFN-α-2a + RBV	
3	Urinary tract infection (antibiotic therapy: Trimethoprim, Norfloxacin)
6	Respiratory infection (antibiotic therapy: Moxifloxacin)
8	Mucosistis oris, angular cheilitis (Cholinsalicylat)
8	Stomatitis aphtosa (antiinfective therapy: Hexetidin)
8	Recurrent bronchitis (antibiotic therapy: Azithromycin)
13	Herpes labialis (antiinfective therapy: Hexetidin, virostatic therapy: Aciclovir)
16	Drug eruption (Methylprednisolon creme)
17	Skin rash (Mometason creme)
22	Cholezystitis (hospitalisation)
37	Bronchitis (antibiotic therapy: Clarithromycin.)
54	Herpes labialis (virostatic therapy: Aciclovir)
Legalon + Peg-IFN-α-2a + RBV	
22	Bronchitis (antibiotic therapy: Amoxicillin and Clavulan acid)

Table 3.8: Clinically relevant infections and infestations during antiviral treatment in patients receiving BOC- and TVR-based triple-therapy. See also Table 3.7

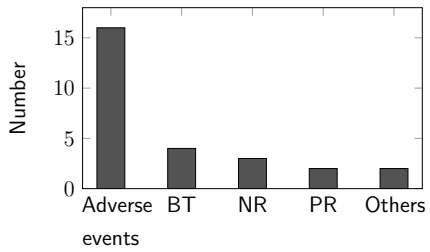
therapy-regimen / week and type of infection or infestation
Peg-IFN-α-2a + RBV + BOC
6 Parodontitis, gum bleeding (antibiotic therapy: Penicillin)
8 Fever of unknown origin (antibiotic therapy: Moxifloxacin)
8 Urinary tract infection (antibiotic therapy: Trimethoprim)
8 Otomycosis (antibiotic therapy: Ciprofloxacin)
11 Parodontitis (antibiotic therapy: Clindamycin)
12 Gastroenteritis, hematochezia (hospitalisation)
14 Influenza (hospitalisation) $\rightarrow$ *discontinuation in week 14*
15 Otomycosis (antimycotic therapy: Itraconazol, Clotrimazol creme)
16 Pleural empyema (antibiotic therapy: Sulfamethoxazol und Trimethoprim)) $\rightarrow$ *discontinuation in week 16*
16 Skin rash (Betamethason creme)
17 Herpes labialis (visrostatic therapy: Aciclovir)
18 Dermatitis (Methylprednisolon creme)
19 Skin rash (Methylprednisolon creme)
21 Parodontitis (antibiotic therapy: Clindamycin)
25 Skin rash (Betamethason creme)
30 Gingivitis (antibiotic therapy: Amoxicillin and Clavulan acid)
31 Angina tonsillaris (antibiotic therapy: Amoxicillin and Clavulan acid)
38 Angina tonsillaris (antibiotic therapy: Amoxicillin and Clavulan acid)
45 Soar throught (antiinfective therapy: Hexetidin)
48 Herpes labialis (virostatic therapy: Aciclovir)
48 Angina tonsollaris (antibiotic therapy: Amoxicillin and Clavulan acid)
Peg-IFN-α-2a + RBV + TVR
1 Drug eruption (antiinfective therapy: Methylprednisolon milk, Betamethason creme) $\rightarrow$ discontinuation in week 1
2 Exanthema (antiinfective therapy: Methylprednisolon creme)
2 Pruritus ani et thoracicus (antimycotic therapy: Nystatin, Zincum oxydatum creme)
2 Exanthema (antiinvective therapy: Zincum oxydatum creme) $\rightarrow$ discontinuation in week 4
4 Rash, pruritus, exanthema (antiinfective therapy: Methylprednisolon creme, Betamethason creme)
5 Drug eruption (Diflucortolonvalerat creme)
5 Urinary tract infection (antibiotic therapy: Trimethoprim)
8 Abscess due to cat's bite (hospitalisation) $\rightarrow$ discontinuation in week 16
9 Pneumonia (hospitalisation) $\rightarrow$ discontinuation in week 9
10 Exanthema, pruritus (Mometason creme)
11 Drug eruption (hospitalisation)
16 Urinary tract infecion (antibiotic therapy not otherwise specified)
21 Skin reaction (Clobetason creme)
21 Skin rash (Cortisone creme)
24 Parotis sinistra, Rhinitis (antibiotic therapy: Amoxicillin and Clavulan acid)
44 Prostatitis (antibiotic therapy: Amoxicillin and Clavulan acid)

3.7 Discontinuation of antiviral therapy

In this section a detailed description about the reason and time-point of treamtent discontinuation is summarized.

Discontinuation of therapy is given if all antiviral medication is stopped prior to the patient's planned EOT. Reasons for discontinuation are given explicitly in Table 3.9 and summarized in Figure 3.25. Average weeks of discontinuation in patients with dual- or triple-therapy regimes are given in Figure 3.26.

Fig. 3.25: Discontinuation



The most frequently reason for treatment discontinuation was the occurance of adverse events (16 cases), followed by insufficient viral response (4, 3, and 2 cases with breakthrough (BT), non-response (NR), and partial-response (PR)), and other causes (2 cases: One patient wished to discontinue antiviral therapy without suffering from any medical discomfort, and another patient suffered from myocardial infarction).

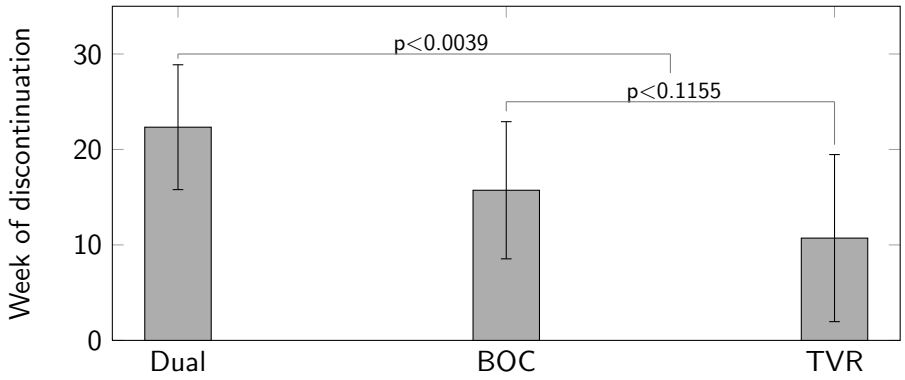


Figure 3.26: Average week of discontinuation in patients receiving dual-therapy or triple-therapy. A significant difference was found between dual- and triple-therapy regimes. Dual, dual-therapy; BOC, Boceprevir-based triple-therapy; TVR, Telaprevir-based triple-therapy.

On average adverse events with triple-therapy regimes are reported to occur significantly earlier than with dual-therapy (week 13.8 ± 8.0 vs. week 22.3 ± 6.5, $p < 0.004$, student's unpaired t-test, two-sided, 95% confidence interval). However, there was no statistical significant difference between BOC and TVR guided triple-therapy regimes.

This probably result from the low number of discontinuations in this subgroups, and/or from the fact that BOC-based therapy starts with a 4 week peg-IFN-α + RBV lead-in.

Table 3.9: Reasons for discontinuation of antiviral therapy. Therapy regime, week and reason for discontinuation are given for patients in which antiviral therapy was stopped before end of treatment was achieved.

therapy-regimen / week and reason for discontinuation	
Peg-IFN-α-2a + RBV	
16	Adverse events (cephalea, weight gain, depression, sweating)
16	Viral non-response
23	Patient's wish (no medical discomfort reported)
24	Viral partial-response
26	Adverse events (dry skin, paresthesia, alopecia, fatigue, melancholy)
29	Viral non-response
32	Adverse events (depression)
Peg-IFN-α-2b + RBV	
23	Viral partial-response
Legalon + Peg-IFN-α-2a + RBV	
12	Viral non-response
Peg-IFN-α-2a + RBV + BOC	
6	Adverse events (Staphylococcus sepsis)
7	Adverse events (gastroenteritis)
8	Adverse events (depression, Soor-stomatitis, anemia)
12	Adverse events (bloody and purulent secretion out of nose, depression, aggressiveness)
14	Adverse events (influenza)
16	Adverse events, wish of patient and family doctor (emesis, diarrhoe)
18	Adverse events (syncope, anemia)
18	Adverse events (pulmonary infection with Nocardia)
22	Viral breakthrough
24	Viral breakthrough
28	Viral breakthrough
Peg-IFN-α-2a + RBV + TVR	
1	Adverse events (TVR-related rash)
4	Adverse events (chill, cephalea, nausea, exertional dyspnoea)
8	Adverse events (hematologic TVR-intolerance), *continuation with dual-therapy*
8	Myocarial infarction
9	Adverse events (acute hepatic decompensation)
19	Adverse events (abscess at toe due to a cat's bite)
26	Viral breakthrough, *continuation with dual-therapy*

3.8 End of treatment

Eventually, SVR-rates with respect to HCV-genotype, therapy regime, gender, viral-load, and treatment duration are discussed.

The EOT is the particular date when the patient intended stopped all antiviral treatment according to the treatment schedule. Follow-up was only recorded when EOT was achieved. Thus adverse events which appear later to treatment discontinuation are not assessed as treatment related adverse events.

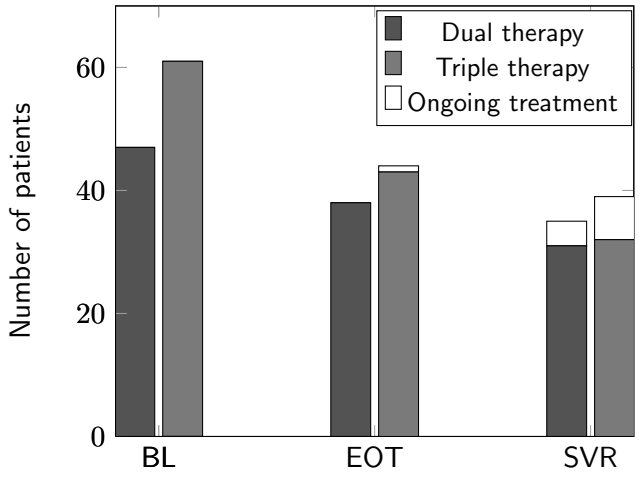
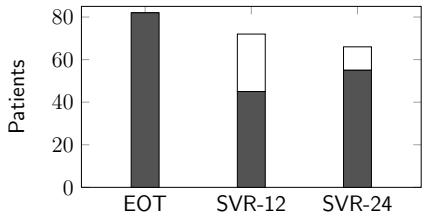


Figure 3.27: Number of patients during antiviral therapy. At End Of Treatment (EOT) 1 triple-therapy patient has not finished the scheduled therapy regimen; another 4 and 7 patients with dual- and triple-therapy have not reached their scheduled date at follow up week 24 post EOT, respectively. BL, baseline; EOT, end of treatment; SVR, sustained virological response.

The number of patients during antiviral therapy is given in Figure 3.27. The count at baseline was 47 with dual-therapy and 61 with triple-therapy (patient's from both BOC- and TVR-based therapy). At the end of data acquisition 82 patients have already reached their end of treatment. In 25 patients antiviral therapy has to be stopped before they could have reached their EOT. One patient (TVR-based triple-therapy) has not reached EOT during survey period. Overall[1] SVR was already reached in 72.1% and 59.2% of cases for dual- and triple-therapy, respectively. SVR refers here to Sustained virological responce 24 weeks past end of treatment (SVR-24). If there was no clinical contact 24 weeks past EOT documented, SVR-12 was used instead.

[1] all HCV-genotypes included

Fig. 3.28: SVR-12 vs. SVR-24



Patients who have eradicated HCV at their EOT (i.e. undetectable HCV-RNA in a sensitive assay) have a 87.5% chance to reach SVR-12 and a 85.0% chance to reach SVR-24. However, if SVR-12 was achieved a sustained virological response at follow up week 24 was reached in 97.1% of cases (see Figure 3.28. White bars represent patients who have had undetectable HCV-RNA and did not appear at the distinct control at follow up week 12 or 24. Percentage is calculated only for patients who have been at required appointments.).

In Figure 3.29 the number of patients with and without ability to eradicate HCV (i.e. to achieve SVR) with respect to their treatment duration is given. According to treatement recommendations an HCV-genotype distribution most patients reached their EOT at weeks 22 – 26 and 46 – 50 (compare Tables 1.7 and 1.8).

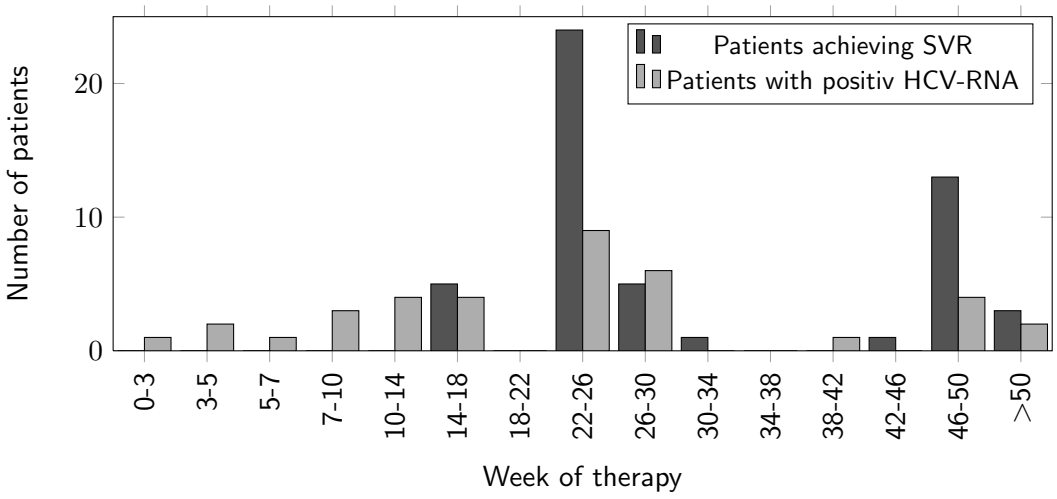


Figure 3.29: Treatment duration and outcome. Overall number of patients reaching Sustained Virological Response (SVR, i.e. undetectable HCV-RNA with an sensitive assay) or still bearing HCV-RNA (i.e. positive HCV-RNA) are shown.

The following figures provide information about SVR-rates depending on gender (Figure 3.31), host IL-28-genotype (Figure 3.33), baseline viral load (Figure 3.30), grade of liver fibrosis/cirrhosis (Figure 3.34), and HCV-genotype (Figure 3.36).

Fig. 3.30: SVR vs. viral load.

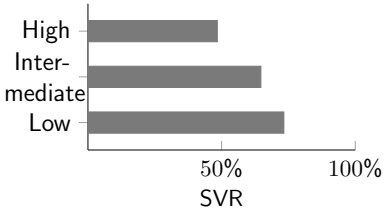


Fig. 3.33: SVR vs. IL-28.

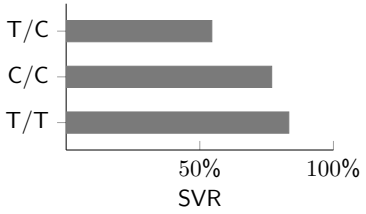


Fig. 3.31: SVR vs. gender.

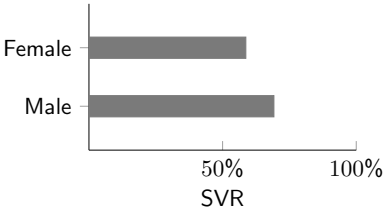


Fig. 3.34: SVR vs. hepatic damage.

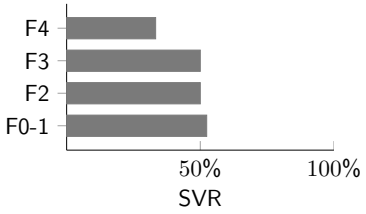


Fig. 3.32: SVR vs. age [years]

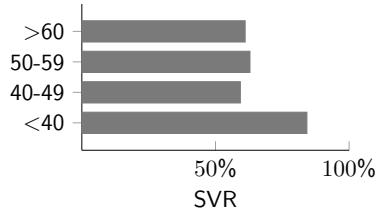
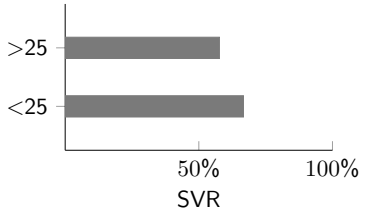


Fig. 3.35: SVR vs. BMI.



A low viral load at baseline ($< 400\,000$ IU/ml HCV-RNA) is associated with a higher chance to eradicate the virus and achieve SVR compared to a high viral load ($> 800\,000$ IU/ml HCV-RNA). The higher the baseline viral load the lower the chances to cure, e.g. 73.3%, 64.7%, and 48.4% for low, intermediate, and high viral load, respectively. (see Figure 3.30).

Host IL-28 genotype T/T has shown to be favorable for treatment success (83.3%, 76.9%, and 54.5% for T/T, C/C, and T/C, respectively, see Figure 3.33). However, there have only been 6 patients bearing this genotype. Thus this result may be imprecisely due to the low number of subjects.

Considering both patients with dual- and triple-therapy, male gender was associated with a better chance for SVR, namely 58.7% in female and 69.2% in male subjects (see Figure 3.31).

Probability to achieve SVR is higher with low fibrosis grading (see Figure 3.34). However, SVR rates in patients with hepatic cirrhosis at baseline were 33.3%, while

SVR rates for patients with absent or mild fibrosis (Metavir F0–F1, Fibroscan $<$ 7.0 kPa) were 52.4%.

Age $<$ 40 years yields to higher SVR rates compared to older subjects (84.2% and 61.3% for $<$ 40 years and $\geq$ 40 years, respectively; see Figure 3.32). However, HCV-genotypes other than 1 were more often present in younger patients (52.6% and 15.0% for $<$ 40 years and $\geq$ 40 years, respectively). Thus a higher SVR-rate in younger patients may be related to a better prognosis in non-genoype 1 patients.

A body mass index (BMI) less than 25 kg/m^2 was related to a higher rate of SVR (66.7% compared to 57.7% for $<$ 25 kg/m^2 and $>$ 25 kg/m^2, respectively; see Figure 3.35).

Documented SVR rates for each HCV-genotype are given in Figure 3.36. Comparable to literature highest SVR rates are for genotype 3, followed by genotype 2, 4, and 1. Lower SVR in triple-therapy may result from the higher number of therapy experienced patients in the triple-therapy subgroup (compare also Table 3.1).

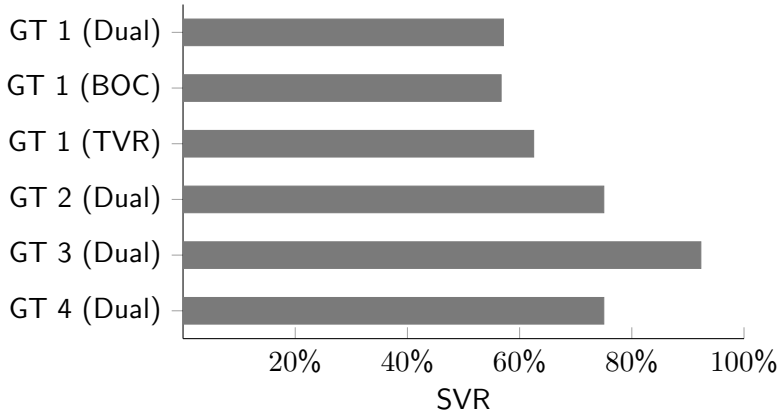


Figure 3.36: Sustaind virological response with respect to HCV-Genotype. SVR, sustained virological response; GT, genotype; Dual, dual-therapy; BOC, Boceprevir-based triple-therapy; TVR, Telaprevir-based triple-therapy.

4 Discussion

This chapter opens with **Treatment algorithm adherence** (➪ page 62) where the patient's compliance, the choice of therapy regime, and the realization of treatment monitoring are illustrated.

Subsequently, in **Subjects** (➪ page 63) the subject's demographic data, the contained HCV-genotype prevalence, the route of HCV-infection, and the baseline viral load are addressed briefly.

The aim of **Adverse events** (➪ page 64) is to discuss statistical measures of all reported adverse events alongside with their incidences. Additionally adverse events reported by more than 10% of patients are summarized.

In **Significant infections and infestations** (➪ page 66) the occurrence of significant infections and infestations as well as discontinuation of antiviral therapy are described

To establish **Sustained virological response** (➪ page 67) is the primary aim of any antiviral therapy.

At last, potential **Limitations** (➪ page 68) and weaknesses of this thesis' study are addressed briefly.

4.1 Treatment algorithm adherence

The patient's compliance, the choice of therapy regime, and the realization of treatment monitoring are illustrated.

Treatment indication

As recommended, all patients suffering from HCV infection meeting no exclusion criteria should be considered for antiviral therapy (compare Section 1.2). Expectedly, the indication for antiviral therapy comply with current guidelines in all patients included in this study.

Treatment algorithm

Although there are several guidelines regarding the treatment of chronic hepatitis C, to the author's knowledge there is no bijective and self-contained chart providing all necessary information. Thus, the author deduced available information and created treatment algorithms for current antiviral treatment regimes (see Appendix, Section 6.1). The decision which regime was applied is strongly influenced by,

Treatment regime

- the HCV-genotype,
- the patient's treatment experience, and
- known risk factors.

Adherence to treatment schedule

Treatment duration is determined by the chosen therapy regime and treatment efficacy (estimated by HCV-RNA measurements at certain time-points). Overall adherence to the treatment schedule was roughly given. However, a tight adherence to recommended time-points (compare Table 1.7) is in fact worthwhile, but a more flexible approach adjusted to the patient's individual necessities seems to be more promising. The occurrence of adverse events, their severity and impact on antiviral therapy, as well as the patient's mental needs have a major impact on treatment progress. In fact, patients included in this study appear much more often to the appointments than recommended (compare Figure 3.11).

Treatment monitoring

At each clinical contact the following parameters are collected repetitively and documented as a handwritten comment within the patient's health record:

- Current date and treatment progress (i.e. week of therapy).
- The patient's general condition and body weight (occasionally blood pressure, heart rate, body height, respiratory frequency, and axillary body temperature).
- Occurred adverse events.
- Current antiviral medication and newly prescribed antiviral medication.

- Date of next scheduled clinical contact.

Within the scope of this thesis the addition of an adverse event grading would have been profitable. In rare cases a typo was found leading to diverging details in the handwritten and electronic health record (primarily discrepancies in body weight).

Digital approach

However the use of a computer based form, accessible by both patient and medical staff may provide advantages:

- Increased individual responsibility of patients, thus possibly a higher therapy adherence.
- A more explicit documentation of adverse events due to a more detailed metering time period (e.g. if the electronic form can be accessed via Internet).
- Improvement of clinical contact duration, since the electronic form can be pre-filled by the patient.
- A statistical evaluation of treatment efficacy and safety can be autogenerated simultaneously.

Additionally an electronic approach may have advantages in future scientific evaluation due to the possibility of an easier and more rapid access to mandatory data.

4.2 Subjects

The subject's demographic data, the contained HCV-genotype prevalence, the route of HCV-infection, and the baseline viral load are addressed briefly.

According to the demographic data of included patients no apparent feature of a HCV-patient can be deduced (compare Section 3.2). Especially age, weight, gender, and appearance of substance abuse is in agreement with a representative middle-european citizen (compare Table 3.1).

Genotype prevalence

According to national prevalence[67], a predominance of HCV-genotype 1 infections was found in the study population, where the majority of individuals is infected with HCV-genotypes 1B (48.5%), 1A (27.8%), and 3A (15.5%, compare Figure 3.2). Surprisingly HCV-genotypes 2 and 4 exclusively appear in female and male subjects,

respectively. This discrepancy may be related to epidemiological, social, and/or demographic factors. Worldwide the highest prevalence of HCV-genotype 4 is in Egypt and northern Africa[1,68]. There may be still a lagged consultation of health care providers in immigrants, especially for women in strictly patriarchal organized cultures. However, due to the limited number of patients in this subgroups, the gender difference in HCV-genotypes found here may rather be by chance than generally valid.

Route of infection

Although the route of infection is not known in the majority of patients, the most frequent source of HCV-infection is the transfusion of blood products that occured somewhere between the 1970's and 1990's (compare Figure 3.5). This result is consistend with a significantly higher prevalence of HCV-infection in patients in Austria who have received blood-products prior to 1991[69].

Baseline viral load

Interestingly but probably by chance, a significant difference of baseline HCV-RNA viral load between female and male patients was found, with male bearing a higher viral load ($p < 0.003$, compare Figure 3.9).

4.3 Adverse events

Statistical measures of all reported adverse events and their incidences are discussed. Additionally adverse events reported by more than 10% of patients are summarized.

Under ongoing therapy the average fraction of patients reporting adverse events was $(67 \pm 18)\%$, $(71 \pm 26)\%$, and $(74 \pm 24)\%$ in dual-therapy, BOC-, and TVR-based triple-therapy, respectively (compare Figure 3.16). The average number of adverse events per week of antiviral therapy was significantly higher in patients receiving triple-therapy when compared to dual-therapy ($p < 0.0004$, compare Figures 3.17 and 3.18). Thus only a few patients were left without suffering from adverse events at each clinical contact (compare Figures 3.15). Overall there was not a single patient who did not suffer from any adverse event during the entire treatment duration.

Reported adverse events and their incidence correspond to data from available literature[58–62] (compare Table 1.12 with Tables 3.2, 3.3, and 3.4). Adverse events reported by more than 10% of patients within this study are commonly known as adverse events

Table 4.1: Adverse events reported by more than 10% of patients in this study.

☐	abdominal pain	☐	fewer
☐	aggressiveness	☐	flue like symptoms
☐	alopezia	☐	loss of appetite
☐	anemia	☐	mucocutaneous alterations
☐	arthralgia	☐	musculoskeletal discomfort
☐	asthenia	☐	myalgia
☐	burning eye	☐	nausea and vomiting
☐	cephalea	☐	neutropenia
☐	chills	☐	nose bleeding
☐	coughing	☐	pruritus
☐	diarrhea	☐	rash
☐	dizziness	☐	sleeping disorders
☐	dysgeusia	☐	sweating
☐	dyspnoea	☐	thrombopenia
☐	emotional lability	☐	xerodermia
☐	fatigue	☐	xerostomia

to HCV-antiviral therapy[22,24,32,36,46–51,63] (see Table 4.1).

As expected, adverse events occurring within the initial 4 weeks of antiviral therapy in a BOC-based regimen are similar to the dual-therapy regime. Thus, the seemingly earlier occurrence of adverse events in TVR-based therapy regimen in comparison with BOC-based regimen may be evoked by the 4-weeks-lead-in in BOC-based triple therapy (compare Table 3.9).

There was no clinically relevant infection or infestations when using peg-IFN-α-2b in any regime. However, there was an insufficient number of patients in this subgroup to draw general conclusions out of this circumstance.

However minor discrepancies between this thesis' results and literature data may be enhanced by a lack of definition regarding HCV-adverse event terminology: The documentation of adverse events is not standardized. Often the patients very words are documented without any medical interpretation of the prevailing signs and symptoms (compare Appendix, Section 6.3).

4.4 Clinically relevant infections and infestations

The occurrence of clinically relevant infections and infestations as well as discontinuation of antiviral therapy are described.

Clinically relevant adverse events can appear at any time-point during the therapy. However, if they occur, it is not undoubtedly likely that the therapy is discontinued. In fact, discontinuation of therapy yields in the overwhelming number of cases from adverse events (16 cases, comprising 59.2% of discontinued cases) but only 6 cases were due to clinically relevant infections and/or infestations. Out of the overall 49 clinically relevant infections and infestations only 6 patients needed to discontinue their therapy. The others being non-infectious adverse events, e.g. cephalea, depression, sweating, alopecia, fatigue, rash, dyspnoea, nausea, anemia, emesis, paresthesia, and dry skin (compare Tables 3.7 and 3.8 with 3.9).

The risk of suffering from clinically relevant infections and/or infestations is higher in triple-therapy compared to dual-therapy (odds ratio 4.5, 95% CI: 2.0 – 10.3, $p = 0.0004$, Fisher's exact test, two-sided) and highest in BOC-guided triple therapy (BOC- vs. TVR-based triple therapy, odds ratio 1.1, 95% CI: 0.4 – 3.1, $p = 1$, Fisher's exact test, two-sided. see Table 4.2).

Table 4.2: Occurrence of clinically relevant infections and/or infestations. DUAL, dual-therapy; BOC, Boceprevir-based triple-therapy; TVR, Telaprevir-based triple-therapy.

	DUAL	BOC	TVR
with relevant infections	12	21	16
without relevant infection	35	13	11

However, the average week of discontinuation is significantly earlier in patients receiving triple-therapy compared to dual-therapy ($p < 0.004$, compare Figure 3.26). Thus leading to the conclusion that patients receiving triple-therapy are more likely,

- to suffer from adverse events at all,
- to evolve clinically relevant infections and/or infestations, and
- to discontinue antiviral therapy.

4.5 Sustained virological response

The aim of antiviral therapy is to eradicate HCV infection, e.g.to establish sustained virological response.

HCV-RNA eradication, e.g. sustained virological response (undetectable HCV-RNA in a sensitive assay), was achieved by 57.1% – 92.3% with dual therapy (depending on HCV-genotype), 56.7% with BOC-based triple-therapy, and 62.5% with TVR-based triple-therapy (compare Figure 3.36). These findings are consistend with recent results of Virlogeux et al. (2014) who found an overall SVR-rate of 59.7% in 186 therapy-experienced and therapy-naïve HCV-patients treated with BOC- or TVR-based triple-therapy[70] and Al-Bawards et al. (2014) who found an overall SVR-rate of 54.7% in 55 therapy-experienced and therapy-naïve HCV-patients receiving TVR-based triple-therapy[71]. However, other trials yield to considerably higher SVR-rates (69.6% overall SVR in TVR-based tripe-therapy[72], 59% – 66% in therapy-experienced patients receiving BOC-based triple-therapy[73], 67% – 68% in therapy-experienced patients receiving BOC-based triple-therapy[74]).

SVR

The overall fraction of patients achieving SVR was highest in the following subgroups (compare Figures 3.34, 3.33, 3.31, and 3.30):

- HCV-genotype 2 or 3.
- Low viral load at baseline (defined as HCV-RNA $< 400.000\,\mathrm{IU/ml}$).
- Male gender.
- Age < 40 years.
- Body mass index $< 25\,\mathrm{kg/m^2}$.
- Low grade of hepatic damage (e.g. low fibrosis grading).
- T/T host IL-28 genotype.

Despite from gender and IL-28 genotype, similiar results are decribed in Huber et al. (2003)[75]. However, HCV-genotypes other than 1 were more often present in younger patients (52.6% and 15.0% for < 40 years and ≥ 40 years, respectively). Thus a higher SVR-rate in younger patients may be related to a better prognosis in non-genoype 1 patients. The result concerning the IL-28 genotype may be misleading due to the few number of subjects in the T/T-subgroup (compare Section 3.8, Figure 3.33).

However, patients who have eradicated HCV at their EOT (i.e. undetectable HCV-RNA in a sensitive assay) have a 87.5% chance to reach SVR-12 and a 85.0% chance

SVR-12 vs. SVR-24

to reach SVR-24. If SVR-12 was achieved, a sustained virological response at follow up week 24 was reached in 97.1% of the cases (compare Figure 3.28).

4.6 Limitations

Potential limitations and weaknesses to this study are addressed briefly.

The weaknesses of this study are the non-randomized design, the pitfalls associated with collection of data from electronic and hand-written charts, and the potential for inadvertently excluding important causative factors in the propensity matching.

Due to the retrospective design of this study, accompanied by the lack of prospective adverse events grading within the accessed health records, sub-group analysis provided in this thesis must be considered with caution.

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6 Appendix

The Appendix comprised:

In **Treatment algorithm** (➪ page 79) current guideline recommendations are deduced into flow-chart-algorithms.

Reference **Limits of laboratory values** (➪ page 6.2) are summarized.

Subsequently **Adverse events classification and terming** (➪ page 84) lists the original German adverse event terms.

6.1 Treatment algorithm

Treatment algorithms are deduced from current guidelines.

Treatment algorithms containing guideline recommendations for Peginterferon + Ribavirin dual-therapy, Boceprevir-based triple-therapy, and Telaprevir-based triple-therapy are summarized in Figures 6.1, 6.2, and 6.3, respectively. Additionally, futility criteria are given in Section 1.3, Table 1.10.

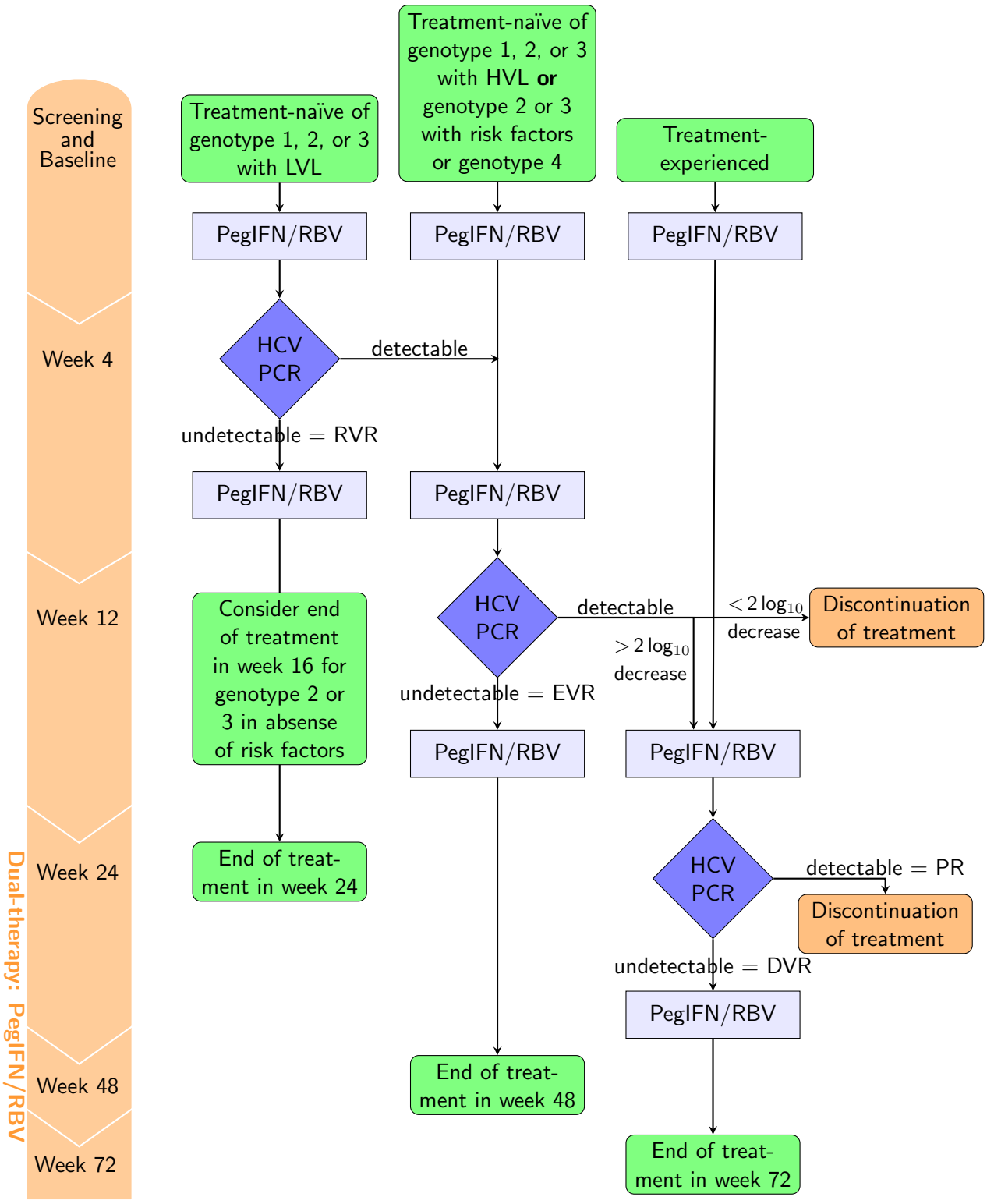

Figure 6.1: Peginterferon/Ribavirin algorithm for both treatment-naïve and treatment-experienced patients with HCV-genotype 1, 2, 3, or 4. LVL, low baseline viral load (< 400 000 – 800 000 IU/ml); HVL, high baseline viral load (> 400 000 – 800 000 IU/ml); Risk factors: advanced fibrosis, cirrhosis, cofactors affecting response (insulin resistance, metabolic syndrome, non-viral steatosis). Futility criteria are summarized in Table 1.10).

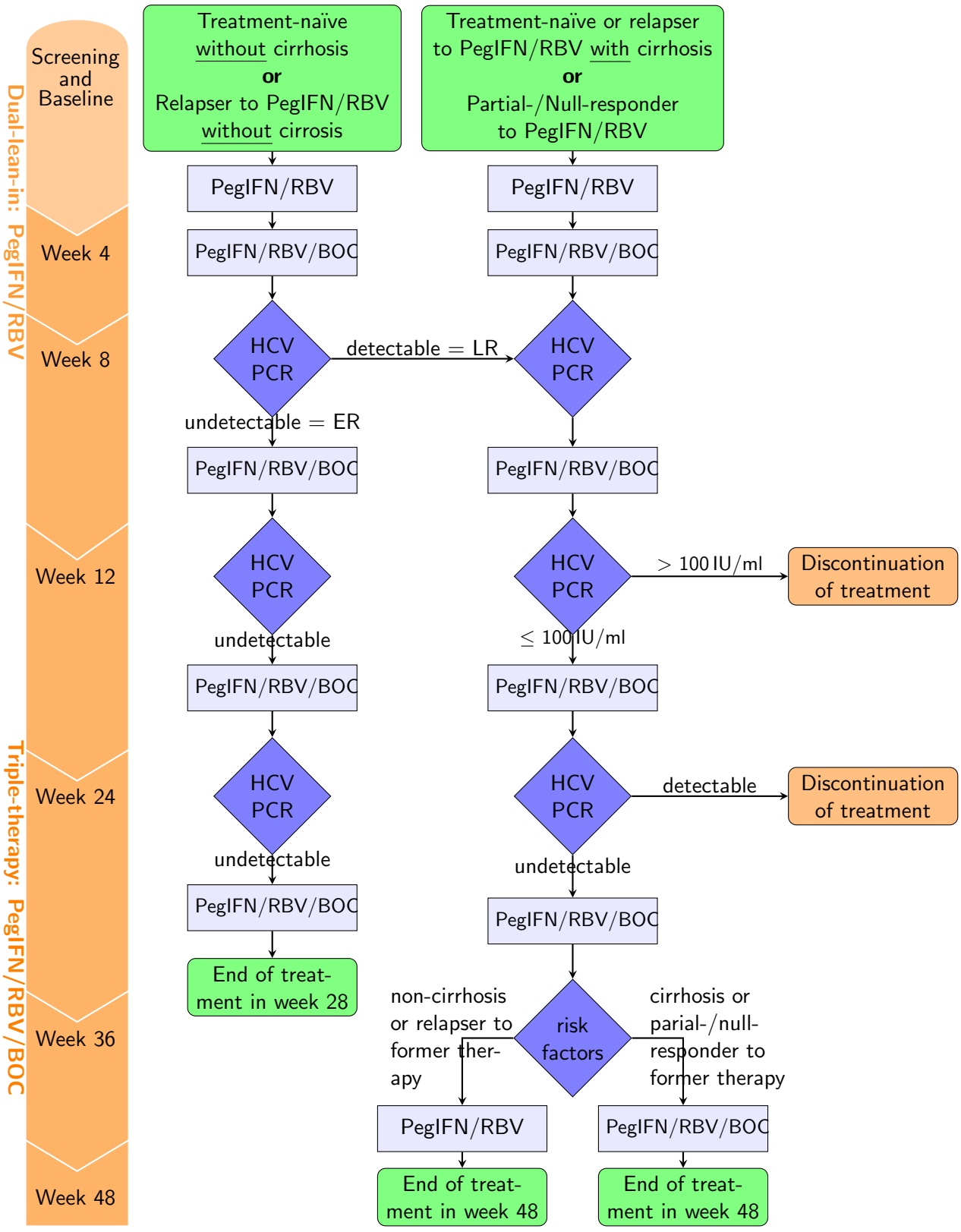

Figure 6.2: Boceprevir/Peginterferon/Ribavirin algorithm for both treatment-naïve and treatment-experienced patients with HCV genotype 1. Futility criteria not included in this figure are: Stop all treatment if HCV RNA rebounds at any timepoint ($\geq 1 \log_{10}$ increase from the nadir HCV RNA) or virological breakthrough occurs (compare Table 1.10).

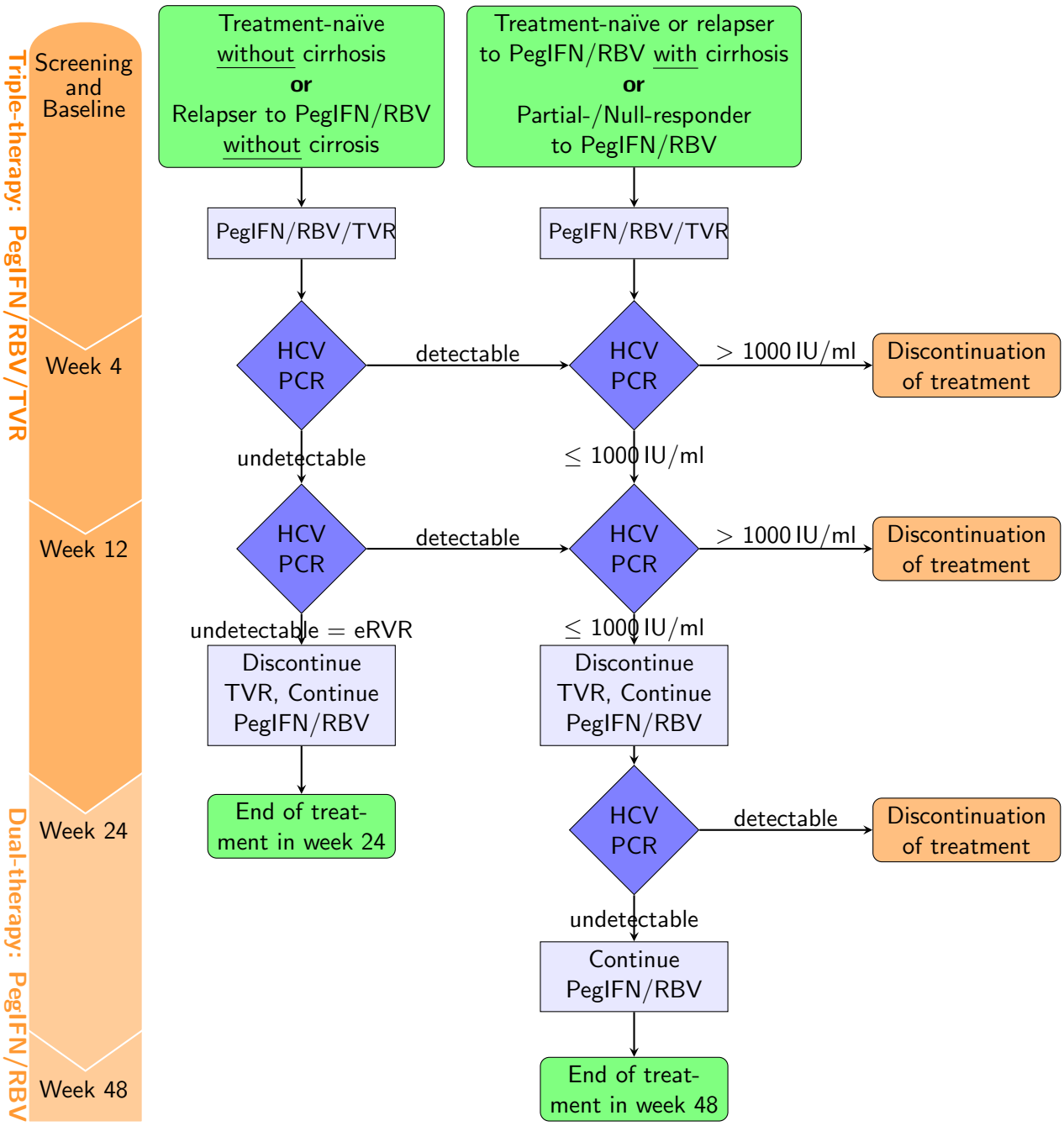

Figure 6.3: Telaprevir/Peginterferon/Ribavirin algorithm for both treatment-naïve and treatment-experienced patients with HCV genotype 1. Futility criteria not included in this figure are: Stop all treatment if HCV RNA rebounds at any timepoint ($\geq 1 \log_{10}$ increase from the nadir HCV RNA) or virological breakthrough occurs (compare Table 1.10).

6.2 Limits of laboratory values

Lower and upper limits of laboratory values used in this thesis.

Table 6.1: Laboratory reference values for female and male adults according to the Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University Graz.

			female		**male**	
Acronym	**Name**	**Unit**	*upper*	*lower*	*upper*	*lower*
ALB	Albumin	g/dl	3.5	5.3	3.5	5.3
ALT	Alanine aminotransferase	U/l		35		45
AP	Alkaline phosphatase	U/l	35	105	40	130
AST	Aspartate aminotransferase	U/l		30		35
BASO	Basophils	%	2	12	2	12
BILI	Bilirubin, total	mg/dl	0.1	1.2	0.1	1.2
BUN	Blood Urea Nitrogen	mg/dl	10	45	10	45
CA	Calcium	mmol/l	2.2	2.65	2.2	2.65
CHE	Cholinesterase	U/l	3900	11000	4600	13000
CHOL	Cholesterol, total	mg/dl		200		200
CK	Creatine Kinase	U/l		145		170
CREA	Creatinine	mg/dl		1		1.21
CL	Chloride	mmol/l	95	110	95	110
CRP	C-reactive protein	mg/l		5		5
EO	Eosinophils	%		5		5
GGT	Gamma Glutamyl Transferase	U/l		38		55
GLUC	Glucose	mg/dl	70	115	70	115
HB	Hemoglobin	g/dl	12	15.3	13	17.5
HCT	Hematocrit	%	35	45	40	50
K	Potassium	mmol/l	3.5	5	3.5	5
LDH	Lactate Dehydrogenase	U/l	120	240	120	240
LY	Lymphocytes	%	20	40	20	40
MCH	Mean corpuscular hemoglobin	pg	28	33	28	33
MCHC	Mean corpuscular hemoglobin concentration	g/dl	33	36	33	36
MCV	Mean corpuscular volume	fl	88	98	88	98
MONO	Monocytes	%	2	12	2	12
NA	Sodium	mmol/l	135	145	135	145
NEUTRO	Neutrophils	%	50	75	50	75
PT	Thrombin Time	%	70	120	70	120
RBC	Erythrocytes	T/l	4.1	5.1	4.05	5.9
RETI	Reticulocyte count	‰	5	20	5	20
THROM	Thrombocytes	G/l	140	440	140	440
TRI	Triglyceride	mg/dl		150		150
TSH	Thyroid-Stimulating Hormone	μU/ml	0.27	4.2	0.27	4.2
UA	Uric Acid	mg/dl	2.4	5.7	3.4	7
WBC	White Blood Cell Count	G/l	4.4	11.3	4.4	11.3

6.3 Adverse events classification and terming

A detailed listing of original german adverse event terms found in the patient's health records.

Teeth and periodontium disorders Gingivitis (Zahnfleischentzündung, Gingivitis), Zahnfleischbluten, Zahnprobleme (Zahnprobleme, Zahnbeschwerden).

Temperature regulation disorders Fieber (febrile Temperaturen, Hyperthermie, Fieber, febrile Reaktion, Fieberschübe), Hitzeunverträglichkeit (Hitzeunverträglichkeit, Hitzeintolleranz), Hyperthermie, Schüttelfrost (Schüttelfrost, Frösteln, Kältegefühl, Kälteempflindlichkeit), Schwitzen (Schwitzen, Hitzewallung, Schweissausbruch, Hitzegefühl), Hitzewallung, Nachtschweiß (Nachtschweiß, nächtliches Schwitzen).

Respiratory disorders Halsschmerzen (Schluckbeschwerden, Brennen beim Schlucken, Halsschmerzen, trockener Hals), Schluckbeschwerden, grippeähnliche Symptome (Infekt, grippaler Infekt, grippale Beschwerden, grippeähnliche Nebenwirkungen, grippig, Verkühlung, Grippe, fieberhafter Infekt), Rhinitis (Rhinitis, verschnupft, verstopfte Nase), Bronchitis (Bronchitis, bronchitische Symptome) Pneumonie (Pneumonie), Parotitis, Angina tonsillaris, Husten (Husten mit und ohne Auswurf, Hustenreiz, Reizhusten, trockener Reizhusten), respiratorische Beschwerden (verschleimte Atemwege, verschleimt, gelbliches Sputum, Luftwegsinfekt, respiratorischer Infekt).

Musculoskeletal disorders Arthralgie (Arthralgie, Gelenksschmerzen, LWS-Schmerzen, LWS-Beschwerden, HWS-Beschwerden, Gelenksteifigkeit), Myalgie (Myalgie, Muskelschmerzen, Ganzkörperschmerz, Gliederschmerzen), Krämpfe (Muskelkrämpfe, Beinkrämpfe, Schmerzen, krampfartig, Oberschänkelkrämpfe, Krämpfe, Krämpfe in Armen, Beinen), muskuloskelletale Beschwerden (Armschmerzen, Beinschmerzen, Kreuzschmerzen, Rückenschmerzen, Schmerzen Fuß, Schmerzen im Arm, Schmerzen in Armen, Beinen, Schmerzen in Fingergelenken, Fingergrundgelenkten, Knie, Schmerzen in Handgelenken, Schulterschmerzen, Schmerzen Becken, Schmerzen Rippenbogen, Schmerzen thorakal, Verspannung der Nackenmuskulatur, Nackenschmerzen, Knochenschmerzen).

Psychiatric disorders Adynamie (Adynamie, Antriebslosigkeit), Depression (Depressio, depressiv, depressive Verstimmung), Burn-out, Aggressivität (leicht reizbar, Aggressivität, Agression, agressiv, Gereiztheit, erhöhte bzw. vermehrte Reizbarkeit, Stimmung gereizt, zornig, zwider), Gereiztheit, nervös, Nervosität (innerer Druck, nervös, Nervosität, Unruhe, Zittrigkeit, ängstlich), ängstlich, Suizidalität (suizidale Gedanken), Stimmungsschwankungen (verstimmt, Gemütsschwankungen, Gemütsstörung, gesenkte Stimmung, getrübte Stimmung, Niedergeschlagenheit, psychischer Zustand labil, Stimmung schlecht, reduzierte Stimmung, Stimmung schwankend, schlechte Stimmungslage, weinerlich, Stimmungsschwankung, Stimmung traurig, Dysthymie, traurige Stimmung, Traurigkeit), Schlafstörungen (Alpträume, Schlafstörungen, Durchschlafstörungen, Einschlafstörungen, Schlaflosigkeit, weniger Schlaf), Hyperventilation.

Loss of efficiency Leistungsminderung, Muskelschwäche (reduzierte Leistungsfähigkeit, Leistungsabfall, Leistungsknick, Leistungsverlust, Erschöpfbarkeit, rasch ermüdbar, körperliche Schwäche, Kraftlosigkeit, Leistungsfähigkeit, verringert Belastbarkeit, vermindert, Schwäche), müde, matt, abgeschlagen (Müde, Müdigkeit, MMA, Mattigkeit, Abgeschlagenheit), Konzentrationsschwäche (Konzentrationsschwierigkeiten, Konzentrationsschwäche, Konzentrationsstörung, Merkschwierigkeiten, Gedächtnisschwäche, langsame Reaktion, Benommenheit), Dyspnoe (Belastungsdyspnoe, Dyspnoe, Atemnot, Kurzatmigkeit, Ruhedyspnoe, NYHA I –IV).

Mucucutaneous disorders Schleimhautveränderungen (Aphten, Brennen der Mundschliemhaut, Brennen im Mund, Aphten im Mund, Aphten auf Zunge, Aphten im Rachen, Bläschenbildung im Mund, Schmerzen auf Zunge, Mundbrennen, Beläge enoral, Beläge im Mund, Belägte Zunge, gerötete Schleimhaut, Schleimhautdefekt, Schleimhautläsion, trockene Schleimhaut), Brennen auf der Zunge (Zungenbrennen, Bläschen auf der Zunge), Mundtrockenheit (trockener Mund, Mundtrockenheit), Nasenbluten (Epistaxis, Nasenbluten, Nasensekret, eitrig, blutig), Herpes labialis (Fieberblase, Herpes labialis, Lippenherpes, herpetiformer Ausschlag), Stomatitis (Soorstomatitis, Stomatitis aphtosa), Mukositis.

Skin and subcutaneous tissue disorders Mundwinkelrhagaden (wunde Mundwinkel, Mundwinkelrhagaden), ekzematöse Hautveränderungen (Schuppenflechte, Schuppung, schuppend, Ekzem), Ausschlag (Exanthem, Ausschlag, bläßchenförmig,

Bläschenbildung am Finger, Effloreszenzen, Hautausschlag, Hauteffloreszenzen, Hautreaktion, Plaque), erythematöse Hautverädnerungen (Erythem, Erythrodermie, Hautrötung, Palmarerythem, Rötung), Dermatitis, lokale Reaktion (Einstichstelle blau, lokale Hautreaktion, lokale Rötung), Hautläsion (Haut offen, Hautablösung, Hautinduration, Hautläsion, Hautrhagaden, Rhagaden, vulnerable Haut), trockene Haut (Hauttrockenheit, Haut trocken, trockene Haut, Xerosis cutis), Psoriasis (Psoriasis, psoriatrische Hautveränderug, Schuppenflechte), Photosensibilität (Photosensibilität, Sonne schmerzt auf Haut, Lichtempfindlichkeit, Sonnenempfindlichkeit, erhöhte Empfindlichkeit Sonnenlicht, verstärkt unter Lichtexposition), Hautveränderungen (Hautbeschwerden, blaue Flecken, Lichen, Hautnebenwirkungen, Hautprobleme, Hautveränderung, Hyperpigmentierung, Pigmentflecken, blasses Hautkolorit, blass), perianale Beschwerden (Fissur am After, perianales Ekzem, perianales Jucken, perianaler Pruritus), Hämorrhiden, Thrombophlebitis (Venenentzündung, Trombohlebitis).

Skin appendage disorders Haarausfall (dünnes Haar, Haarausfall, diffuses effluvium), Nagelveränderungen (Nageldystrophie, Nagelbettentzündung).

Gastrointestinal disorders Durchfall (Durchfall, Diarrhoe, blutige Diarrhoe, flüssige Stühle, Blutbeimengungen im Stuhl), Übelkeit/Erbrechen (Emesis, Erbrechen, Übelkeit, Nausea, Würgereiz, Vomitus, heraufgebrochen, Hämatemesis), Appetittverlust (Appetitlosigkeit, Innappetanz, weniger Appetit, Inappetanz, kann nichts essen, kein Appetit), Magenschmerzen (epigastrische Beschwerden, Magenschmerzen, Magenbeschwerden, Magenkrämpfe, epigastrisches Druckgefühl), Sodbrennen (Reflux, Sodbrennen), Bauchbeschwerden (Druckschmerz im Oberbauch, Ziehen im Oberbauch, Schmerzen Oberbauch, Druck im Oberbauch, Oberbauchschmerzen, Oberbauchbeschwerden, Bauchschmerzen, Bauchbeschwerden), intestinale Beschwerden (Ekelgefühl, Obstipation, Meteorismus, Blähungen, Schmerzen Unterbauch, Völlegefühl, Hämatochezie, Tenesmen), Gastroenteritis (Gastroenteritis, Darmgrippe), Proktitis, Colitis, GI-Blutung.

Nervous system disorders Kopfschmerz (Cephalea, Kopfschmerz, Druck im Kopf, Kopfweh, Migräne), Schwindel (Schwindelgefühl, Vertigo, Schwindel), Geruchsmissempfindungen, Geschmackmissempfindungen (bitterer Geschmack, Dysgeusie, Geschmacksveränderungen, Geschmackstörung, metallischer Geschmack, eigenartiger Geschmack), Parästhesien (Dysästhesien, Parästhesien, Sensibilitätsstörungen, taube Fingerspitzen, Taubheitsgefühl große Zehe, Brennen Füße), Polyneuropathie.

Eye disorders Augenbrenne (Augenbrennen, Augentrockenheit, Augenschmerzen, Augenjucken, Augentränen), Visusprobleme (Sehstörungen, Visusverschlechterung, Visusprobleme, verschwommenes Sehen), Konjunktivitis, Katarakt, Papilleneinblutung.

Ear and labyrinth disorders Otitis (Otitis, Ohrenentzündung, Gehörgang gerötet), Ohren (sonst) (Ohrenrauschen, Ohrenschmerzen, Tinnitus, verschlagene Ohren, zugefallenes Ohr, Gehörsturz, Hörsturz, Ohr zugefallen).

Cardiac disorders and Vascular disorders Bluthochdruck (Bluthochdruck, arterieller Hypertonus), Kreislaufschwäche (Blutdruckabfall, Hypotonie, Kollaps, Kollapsneigung, Kreislaufkollaps, Kreislaufprobleme, Kreislaufschwäche, Synkope), Nykturie (nächtlicher Harndrang, Nykturie), cardial (Herzklopfen, Stechen in Brust, Tachycardie).

Fluid shift Beinödeme (Beine angeschwollen, Beinödeme), Schwellung (Angioödem, Gesichtsschwellung, Lidschwellung, Schwellung, Schwellung in Gesicht, Schwellung an Händen), Pleuraerguss.

Renal and urinary disorders Harnwegsinfekt, urogenital (sonst) (Brennen beim Harnlassen, Dysurie, Hämaturie, Makrohämaturie, Flankenschmerz, Prostatitis, Hodenschmerzen, Priabismus), starke Menstruation, Impotenz.

Metabolism and nutrition disorders

Immune system disorders Lymphadenopathie, Immunthyreopathie, Splenomegalie.

Labory value manifestations Hämolyse, Hyperurikämie, Hypokaliämie, Bizytopenie, Hyperurikämie, Panzytopenie, Hypertriglyzeridämie.

Blood and lymphatic system disorders Anämie (Anämie, Eisenmangelanämie), Leukopenie, Neutropenie, Thrombopenie (Thrombozytopenie, Trombopenie).

Hepatobiliary disorders Aszites, Hyperbilirubinömie/äurie, Ikterus (Ikterus, ikterisches Zustandsbild, Sklerenikterus, Dunkelfärbung des Harns), Pruritus (Pruritus, Juckreiz, Jucken, juckend, Hautjucken, Kopfjucken, juckende Kopfhaut, Kratzeffloreszenzen), Cholezystolithiasis.

Infections and infestations Otitis, Harnwegsinfekt, Dermatitis, Prostatitis, Colitis, Konjunktivits, Otomykose, Bronchitis, Pneumonie, Gastroenteritis, Thrombophlebiits, Stomatitis, (grippaler) Infekt, Herpes, Parotitis (Speicheldrüsenentzündung, Parotitis), Thrombophlebitis, Angina tonsillaris, cholezystolithiasis, Abszess, Lungenemphyem.