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Hepatitis C

**Risks, prevention and
treatment**

ELPA



**European Liver
Patients
Association**

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Dear patient,

This booklet is intended to help you to find out more about your disease and to deal with it better. We hope it will encourage you to continue to socialise normally as before, and not to have unfounded fears about transmitting the disease. With the help of the booklet, we would also like to tell you how chronic hepatitis C affects your health, and make you aware of the options for treatment. We hope that we can be of help to you in this way. Please contact the doctor treating you to discuss in confidence any other questions you may have.

A handwritten signature in black ink, appearing to read 'Nadine Piorkowsky'.

*Nadine Piorkowsky
President, ELPA*

A handwritten signature in black ink, appearing to read 'Stefan Zeuzem'.

*Prof. Dr. Stefan Zeuzem
Scientific Advisory
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Contents

Introduction	p. 4
The liver	p. 5
Viral hepatitis C	p. 6
Transmission	p. 7
Complications of hepatitis C	p. 8
Blood tests	p. 10
Liver biopsy (liver tissue sampling)	p. 11
Treatment of hepatitis C	p. 12
Are there alternative therapeutic options?	p. 19
Future therapeutic options	p. 20
Is there a vaccine against hepatitis C?	p. 21
What do I have to bear in mind in relation to my diet?	p. 22
Hepatitis C and pregnancy	p. 22
About ELPA	p. 23

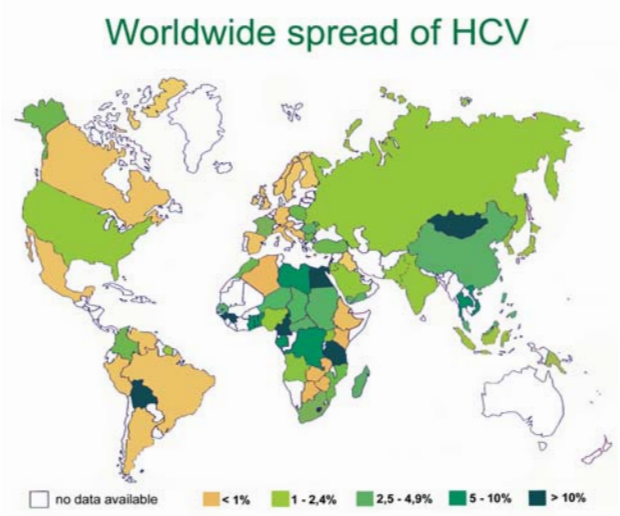
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Introduction

Many millions of people in Europe suffer from chronic liver disease. Cirrhosis of the liver (changes to the liver as scarring develops) is one of the four most common disease-related causes of death in adults aged between 30 and 50 years of age.

Besides alcohol, chronic liver disease is mainly caused by virus-induced hepatitis B and C. The term hepatitis means an inflammation of the liver.

In Europe the anticipated number of new hepatitis B and C infections every year runs to several thousand. The spread of infection with the hepatitis C virus is estimated at 0.5–5% (5–50 out of 1,000 inhabitants), depending on the country.



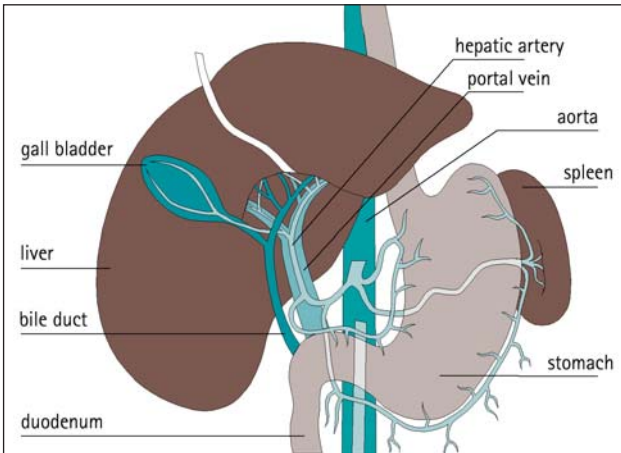
The liver

The liver weighs around 1,500g and is the largest internal organ in the human body. It is located in the right upper abdomen and is surrounded by a connective tissue capsule.

The liver is the central metabolic organ of the body. One of its functions is to break down toxins which are absorbed into the body via the intestines, before they reach the primary circulation system. This is where nutrients entering the liver via the intestines are processed. The liver produces essential proteins, which are necessary for example for blood clotting and warding off infections.

Another important function is the production of bile, which travels to the duodenum via a special system of ducts. The bile eliminates waste matter from the red blood cells and makes the digestion of fat possible. Various toxins are also excreted from the body via bile.

There are no nerve fibres in the liver itself to transmit pain. However, pain may be caused by tension in the connective tissue capsule, if the liver becomes swollen or scarred as a result of inflammatory processes.



Location of the liver in the upper abdomen and its blood supply. The nutrient-carrying blood from the intestines reaches the liver via the portal vein.

Viral hepatitis C

Hepatitis C is a viral infection of the liver. The cause is the hepatitis C virus. The virus multiplies in the liver and is released into the blood by the liver cells. In around 60–80 % of patients, the body's own defence system is unable to fight the virus successfully, and the hepatitis C becomes chronic. In the other 20–40 % of patients, hepatitis C is cured within six months of infection without treatment.

Symptoms of hepatitis C

The symptoms of hepatitis C are very vague, and most patients are not aware of the infection at all. Some patients feel increased tiredness, feel exhausted and debilitated or have right-sided upper abdo-

minal symptoms. The development of jaundice tends to be rare.

Disease mechanism

In a chronic infection, the hepatitis viruses keep infecting more and more liver cells. White blood cells migrate into the liver tissue as a sign of inflammation. They ensure that infected and dead liver cells are destroyed and cleared away. However, they are usually unable to eliminate the virus itself. The dead liver cells may be replaced later by connective tissue (= scar tissue). When connective tissue starts forming in the liver, the early stage is called hepatic fibrosis, and the later stage is called liver cirrhosis. The body is unable to convert scar tissue into liver tissue.

Transmission

The hepatitis C virus is usually transmitted via direct or indirect blood contact (parenteral transmission). Before 1990 it was not uncommon for the hepatitis C virus to be transmitted via blood and coagulation products. The modern test methods used today are able to identify hepatitis C-positive blood donors. The residual risk of hepatitis C infection via a blood transfusion is very slight nowadays.

The virus may also be transmitted through the use of dirty syringes, e. g. in drug use. Other risk factors for infection with the hepatitis C virus are tattoos and

body piercing. Transmission via open wounds, razor blades or toothbrushes is also possible. The virus can be transmitted by sexual contact. However, the risk for sexual partners of infected patients is rated as low. The risk of transmission depends on sexual behaviour.

To date there have been no reports of virus transmission via intact skin or saliva. There is no fear of infection via crockery, glasses or cutlery, provided they are not contaminated with blood.

Complications of hepatitis C

Patients with chronic hepatitis (inflammation of the liver where there are clear signs of inflammation in the liver tissue) have around a 30 % chance of developing cirrhosis in subsequent years. The risk of developing cirrhosis depends among other things on the age of the patients at the time of infection and the duration of the disease, that is, the disease often progresses more rapidly in an infection at a higher age (over 40 years). Factors which may accelerate the development of cirrhosis include other chronic hepatic diseases, for example with other hepatic viruses (e.g. co-infection with the hepatitis B virus) and exposure to substances that damage the liver in other ways. The main culprit here is alcohol.

Cirrhosis is defined as a condition in which a large part of the liver tissue has been replaced by connective tissue. This destroys the normal structure of the liver tissue. This can affect the blood supply, causing high blood pressure in the portal vein (the vein between the intestine and liver). Backflow of blood

may cause dilated veins (varices) to develop in the oesophagus (food tube) and stomach. If these veins burst, severe gastrointestinal bleeding may occur. The risk of bleeding is increased by the fact that the blood's ability to clot is impaired by the reduced synthesis of protein in the liver and a reduction in the number of blood platelets (thrombocytes). Accumulation of body fluids (ascites) in the abdominal cavity may also occur, one reason being the high blood pressure to the liver.

If cirrhosis is present, the liver may be unable to break down some of the toxins entering the blood from the gastrointestinal tract, allowing these toxins to enter the main circulation. These toxins may cause increased fatigue and poor concentration (hepatic encephalopathy, encephalon = brain).

Reduced protein production in the cirrhotic liver impairs blood coagulation and also results in an undersupply of substances needed for the body's defence system. As a result, the patient is more susceptible to infections.

Retention of bile in patients with severe liver disease commonly causes yellowness of the eyes and skin (jaundice). This is often accompanied by itching. At the same time dark urine may be produced. Patients with a long history of chronic hepatitis C also have a greater risk of developing liver cancer (hepatocellular carcinoma). Most patients develop hepatocellular carcinoma secondary to cirrhosis, but there are a few reports of liver cancer occurring in patients with chronic hepatitis C who had no history of cirrhosis. Regular ultrasound scans and blood tests are therefore recommended for these patients. In some cases, hepatitis C is so severe that a liver transplant may be required.

Blood tests

The Hepatitis C virus can be detected in the blood directly via its genetic information (RNA) or indirectly via the antibodies which are formed by the patient's white blood cells. Positive RNA evidence indicates active disease, while the presence of antibodies against the hepatitis C virus (anti-HCV) does not differentiate between a healed up hepatitis C infection and an existing chronic infection. Antibodies can therefore still be detected for a long time in patients who have been cured of Hepatitis C, but not HCV-RNA.

The diagnosis of hepatitis C is based on evidence of hepatitis C antibodies (anti-HCV). If a patient is anti-HCV-positive (that is, he has hepatitis C virus antibodies in the blood), the virus should be directly detected e.g. with a so-called PCR (polymerase chain reaction). This is a particularly sensitive test to detect hepatitis C viruses in the blood.

Whenever antiviral therapy is considered, it is also useful to determine the amount of viruses in the blood (viral load) and the genotype of the hepatitis C virus.

The liver values (ALT, AST, also called transaminases) give information, with certain limitations, about the inflammatory activity of hepatitis. However, normal liver values do not mean that chronic hepatitis C can be ruled out. Liver values are also determined to monitor progress of the disease during treatment.

Since patients with chronic hepatitis C are at greater risk of developing liver cancer, alpha-fetoprotein, a tumour marker for liver cancer, should be monitored at regular intervals (every six to twelve months). Ultrasound scans of the liver should be done at similar intervals.

Liver biopsy (liver tissue sampling)

In order to estimate the extent of connective tissue infiltration, inflammatory activity and the degree of fatty degeneration in the liver, liver biopsy is recommended. Biopsy of the liver involves the removal of a small piece of tissue under local anaesthetic for histological examination under a microscope. A complete histological examination shows the inflammatory activity (grading) and the fibrosis stage (staging) separately.

“Healthy” hepatitis C carriers (viruses detected in the blood, normal liver values and normal liver tissue sample) are rare. The majority of patients, even with normal liver values, show signs of chronic hepatitis in the liver tissue.

Treatment of hepatitis C

In order to halt or to slow down the progress of the disease, therapy can be administered responsibly with interferon alpha, preferably in combination with ribavirin.

Ribavirin is a substance which inhibits mechanisms of hepatitis C viruses which are not yet fully understood. It is effective particularly in combination with interferon alpha and is taken as a tablet or capsule. Interferon is a protein produced naturally by the body, e.g. by the white blood cells, especially when the body has to defend itself against disease-causing organisms. The interferon alpha used to treat viral hepatitis is produced by biotechnology. Like, for instance, the insulin used to treat patients with diabetes, interferon alpha is injected into the fatty tissue layer below the skin.

In order to improve the response rate and the tolerability of therapy with interferon alpha, interferons can be attached to polyethylene glycol (PEG) (pegylated Interferon alpha, peginterferon alpha). Interferons modified in this way have a longer duration of action in the body and only need to be injected once per week.

The polyethylene glycol surrounds the interferon alpha like a protective sheath and thus stops the drug from being broken down prematurely. However, this does not block the sites important for the antiviral effect of interferon. This maintains its effective range more consistently and steadily inhibits the multiplication of the virus over a long period.

Another technology used to prolong the effect of interferon alpha is attaching it to human serum albumin. Albumin is a natural substance with a long

half-life, which has many functions in the body. Interferon alpha linked to albumin (albinterferon) has the antiviral effectiveness of interferon, but only has to be injected every two to four weeks because of the long half-life of albumin. Clinical studies have shown that the long-term virologic response rates in patients with chronic hepatitis C are significantly better with long-acting interferon preparations than with short-acting standard interferons. Cure rates can be increased further by the combination of long-acting interferons with ribavirin. This combination is also superior to the combination of standard interferons with ribavirin in relation to tolerability.

The recommended dosages of interferons are shown in the table on this page. Your doctor should decide on the ribavirin dose on an individual basis, taking into account your blood count (particularly the red blood pigment [haemoglobin]), your weight and the HCV genotype. The dose typically lies between 800 and 1,200 mg daily, divided into two doses, one in the morning and one in the evening. A higher dose can be considered in patients

Standard dosages of interferons

Interferon alpha-2a	3–6 million units three times weekly
Interferon alpha-2b	3–5 million units three times weekly
Peginterferon alpha-2a	180 µg once weekly
Peginterferon alpha-2b	1.0–1.5 µg/kg body weight once weekly
Albinterferon alpha-2b	900 µg once every 2 weeks

who are particularly heavy. In infections with HCV genotype 1 and 4, the ribavirin dose should be around 15 mg per kg body weight, and in genotype 2 and 3 around 13 mg per kg body weight.

The primary aim of treatment is to prevent the disease progressing in patients affected (prevention of connective tissue multiplication [cirrhosis] in the liver and its complications). This aim is best achieved if the hepatitis C virus is completely eliminated from the body, i.e. when the most sensitive methods no longer detect the HCV-RNA in the long term. The response rate (number of patients in whom no viruses are detected in the blood during therapy) of therapy with long-acting interferons and ribavirin is around 60–90 %. Unfortunately the virus reoccurs in some patients who have initially responded to therapy, in some cases even during the treatment (rare) or after discontinuing the drugs. Overall therefore the long-term therapeutic success rate of combination therapy with long-acting interferons plus ribavirin is 50–60 %.

It is particularly important that the drugs are taken regularly. If severe side effects (e.g. depression) occur under therapy with interferon alpha/ ribavirin, these should be treated with drugs if required, but the antiviral drugs should be continued, if possible. Since the side effects of interferon alpha/ribavirin therapy rapidly subside when therapy is completed, the accompanying therapy can be discontinued.

Treatment is particularly successful when therapy is started as early as possible. Acute hepatitis C can be prevented from becoming chronic with 24 weeks of monotherapy with (peg)interferon alpha. In order to achieve this, therapy of acute hepatitis C should

be begun no later than three to four months after the time of infection.

Treatment of chronic hepatitis C is more successful in younger patients and in short-term disease than in older patients who have already reached the stage of cirrhosis. In addition, the likelihood of a long-term virologic response (cure) to combination therapy in patients who are infected with HCV genotype 2 or 3 is significantly better than in patients who are infected with HCV genotype 1 or 4. The duration of therapy also has a major effect on the success of treatment in chronic hepatitis C.

The current guidelines (2009) on the therapy of chronic hepatitis C recommend 24 weeks of standard therapy for patients with HCV genotype 2 or 3; at best this can be reduced to 16 weeks (patient of normal weight, no cirrhosis, low viral load before the start of therapy and rapid virologic response with no evidence of HCV-RNA at therapy week 4). Patients with HCV genotype 2 or 3 who still show HCV-RNA in the blood at therapy week 4 may benefit from therapy lasting more than 24 weeks (36–48 weeks).

The standard duration of therapy for patients with HCV genotype 1 or 4 is 48 weeks, but this can be reduced to 24 weeks in patients (without cirrhosis) who show a low viral load before therapy and have no detectable HCV-RNA in the blood after four weeks of therapy, without reducing the chances of a long-term virologic response. Patients with HCV genotype 1 or 4, who show a slow response to anti-viral therapy with a long-acting interferon and ribavirin (HCV-RNA still detected at therapy week 12, but negative at therapy week 24), appear to benefit from extending therapy to 72 weeks.

With the aid of the viral load at the start and the initial drop in the viral load in the blood, a statement can be made after four and twelve weeks about the extent to which the patients treated have a good chance of the virus being eliminated long-term.

The quicker and more pronounced the initial drop in the viral load, the better the chances of cure. Patients who do not achieve at least a 99 % drop in the initial viral load in the first 12 weeks have little chance of the virus being eliminated in the long term. Various studies have shown that successful combination treatment with interferon and ribavirin reduces the amount of connective tissue fibres in the liver and reduces the development of hepatic cancer. But even when the hepatitis C virus has been eliminated completely, the risk of hepatic cancer remains raised for many years. Therefore regular ultrasound scans of the liver are recommended even after successful therapy.

In principle, antiviral treatment is recommended for all patients with chronic hepatitis C and increased inflammatory activity in the liver, provided that there are no additional diseases or other circumstances which would prohibit such therapy. The doctor treating you should always decide on an individual basis about the preparations, the dose and duration of treatment.

What side effects can be expected in therapy with interferon alpha and ribavirin?

Side effects are common at the start of interferon-alpha treatment and usually become much less severe as treatment progresses. The most common side effects are flu-like symptoms such as fever, headaches, pains in the joints and muscles, fatigue, lack of appetite and weight loss. Thyroid dysfunction occasionally occurs. Some patients suffer from particularly dry skin or temporarily lose their hair during treatment. Mood changes to the point of depression may also occur. Other important side effects are changes in the composition of the blood, especially with regard to the white blood cell count.

Allergic symptoms can be triggered by both interferon alpha and ribavirin. The most common side effect of ribavirin is known to be a temporary lack of red blood cells (anaemia). Regular monitoring of the blood count is therefore essential.

Patients should talk to the doctor treating them regularly during therapy and tell him in detail about any side effects. Many side effects of interferon alpha/ribavirin combination therapy can be helped by adjusting the dose or by (temporarily) prescribing additional drugs. All options should always be explored before therapy is discontinued completely on account of intolerance or side effects.

On no account can it be ruled out that ribavirin may cause the risk of foetal abnormalities to be increased. Patients receiving therapy with ribavirin must therefore use a safe method of contraception during therapy and for up to six months after therapy.

Women who are pregnant before the start of therapy cannot receive the therapy.

What must be considered during therapy with interferon alpha and ribavirin?

During therapy with interferon alpha and ribavirin, liver values (GPT, GOT), the blood count and thyroid values should be regularly monitored. In addition, the viral load (HCV-RNA) in the blood should be measured after four and twelve weeks of therapy (if required, also after 24 weeks). A rapid virologic response (RVR) is referred to when no more HCV-RNA is detected in the blood at therapy week 4 using a sensitive test method. At therapy week 12 a distinction is drawn between a complete early virologic response (cEVR) and a partial early virologic response (pEVR). In a complete response (cEVR), no HCV-RNA is detected in the blood in week 12, whereas in a partial response (pEVR), the viral load at week 12 has fallen against the viral load before the start of therapy by a factor of 100, but HCV-RNA is still detected in the blood. Using the HCV-RNA results at therapy week 4 and 12, an assessment can be made of whether the therapy can be successful and how long it should be continued.

Are there alternative therapeutic options?

Therapy with interferon alpha alone or in combination with ribavirin is currently the only option for removing the hepatitis C virus from the body in the long term. Besides this, there are many reports of success with so-called alternative substances. However, there are no controlled studies in which the effectiveness of such preparations was investigated. Therefore all information relating to these substances is based on non-controlled experiential reports.

Substances used to treat hepatic diseases include for example milk thistle extracts (silymarin), artichoke preparations and glycyrrhizin, which is used predominantly in south east Asia.

Certain silymarin preparations (silibi-

nin) can reduce the viral load when administered in a high daily dose intravenously. However, it is as yet unclear whether the substance is safe in this dose and not only reduces the viral load but also improves upon the cure rates of therapy with peginterferon/ribavirin. When taken in the standard dosages as



Illustration: Milk thistle

a tablet, silymarin has no effect on the multiplication of the virus.

All herbal and other alternative preparations can have dangerous side effects, damage the liver or develop interactions with other drugs. Patients should always tell the GP or specialist treating them about other preparations they have taken, so that the doctors can comment on their tolerability and any possible risks.

Future therapeutic options

Various therapeutic approaches are currently being clinically investigated, including inhibitors of HCV-specific enzymes, which are responsible for the virus multiplying (rotease, helicase, NS5A and polymerase inhibitors). Two HCV-protease inhibitors (boceprevir and telaprevir) are at the furthest stage of clinical development, which in combination with peginterferon alpha and ribavirin can improve the long-term virologic response rates in genotype 1-infected patients by around 20% to approx. 70–75%. It is anticipated that these two substances will receive marketing authorisation in Europe in 2011/2012. Other developments include so-called immunomodulators and drugs which inhibit structures produced naturally in the cell which are involved in the virus multiplying, and therapeutic vaccines, i. e. vaccines which should help the body's immune system to eliminate the hepatitis C virus or slow down the progress of the disease.

There is hope in the long term that it will be possible to treat the hepatitis C virus successfully without injections of interferon. However, combinations of at least two to three inhibitors would be required for this. An important factor in the new substances is that, either alone or in combination, they inhibit any so-called resistant variants of the hepatitis C virus. To sum up, it must be stressed that no new substances will receive marketing authorisation unless comprehensive data is available from clinical trials in relation to efficacy, tolerability and safety. Patients who are interested in receiving these drugs of the future today already should contact large liver centres and obtain information about on-going therapy protocols.

Is there a vaccine against hepatitis C?

A vaccine is only available against hepatitis A and B, but not against hepatitis C. It is probably unlikely that an effective protective vaccine against hepatitis C will become available in the foreseeable future.

If you have not had hepatitis A or B, you should have yourself vaccinated against both these viruses. It is essential that you discuss this issue with your doctor, since an acute co-infection with the hepatitis A or hepatitis B virus can have particularly severe consequences for patients with chronic hepatitis C.

What do I have to bear in mind in relation to my diet?

So long as the liver function is not affected, no special diet is required in chronic hepatitis C. If liver function is impaired, consumption of protein (meat and dairy products) and salt may need to be limited. Your doctor should discuss this with you, possibly with the support of a dietician. It is important for you to avoid alcohol.

Hepatitis C and pregnancy

The risk of the hepatitis C virus being transmitted from the mother to the child during pregnancy is rated as low. The disease is generally not transmitted until during delivery. However, the likelihood of the newborn being infected with the hepatitis C virus is below 5%. The likelihood of transmitting the hepatitis C virus is higher in patients who are also infected with the AIDS virus (HIV).

Opinions differ as to whether hepatitis C infection can be transmitted by breastfeeding. However, most paediatricians do not generally discourage HCV-infected mothers from breastfeeding.

About ELPA

ELPA emerged from a desire amongst European liver patient groups to share their experiences of the often very different approaches adopted in different countries. In June 2004, 13 patient groups from 10 European and Mediterranean Basin countries met to create the association. ELPA was formally launched in Paris on April 14th 2005 during the annual conference of the European Association for the Study of the Liver (EASL) and now has 21 members from 17 countries.

ELPA's aim is to promote the interests of people with liver disease and in particular:

- to highlight the size of the problem;
- to promote awareness and prevention;
- to address the low profile of liver disease as compared to other areas of medicine such as heart disease;
- to share experience of successful initiatives;
- to work with professional bodies such as EASL and with the EU to ensure that treatment and care are harmonised across Europe to the highest standards.

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