

MICE TIMES

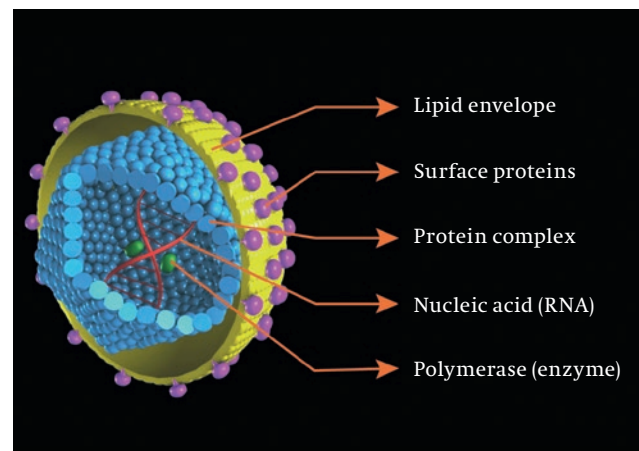
Curing hepatitis C – a quantum leap in medicine

Hepatitis C is an insidious and, as a result, much feared disease. Experts like to call it a silent epidemic, because it affects sizable sections of the population – unknown to many of those affected. Until recently, treatment was difficult and, in view of the side effects, was a burden for many patients – with rather modest prospects of a cure. A group of novel medicines has completely changed the prospects for those affected. The chances of a cure have risen to well over 90 percent – and that with a treatment duration of normally 6 to 12 weeks and tolerable side effects. It is a spectacular success for pharmaceutical research and marks a quantum leap in medicine. Further hope comes from initial vaccine trials.

Sometimes it takes many steps to achieve a substantial improvement in the lot of those affected by a disease. Diabetic patients, for example, live much better today than they did ten or even twenty years ago, although there have been no spectacular advances in the treatment of this chronic disease. Nevertheless medicine is also repeatedly throwing up some resounding successes which turn a fatal disease into a chronic controllable disorder, enabling the patient to live without major restrictions, or which even cure a fatal disease altogether. The latter includes a range of new active substances for the treatment of hepatitis C.

Worldwide between 130 and 170 million people are infected with hepatitis C virus. That is around three percent of the world population. This compares with about 35 million infected with HIV. And in many countries, more people today die of hepatitis C than of AIDS. The hepatitis C virus is transmitted almost exclusively in the blood. Thus by the early 1990s, contaminated blood or blood products (such as clotting factor products) were the primary cause of new infections. Since the identification of hepatitis C virus in 1989 and the development of tests, however, the blood held in blood banks has been carefully monitored, so the risk of infection is as good as excluded. Today, the virus is usually transmitted through the shared use of syringes among drug addicts or through the use of instruments contaminated with hepatitis C virus, e. g. in inappropri-

ate tattooing or piercing procedures. The transmission of infections through sex or from mother to child is rare.



Hepatitis C virus

Life-threatening in the long run

In three-quarters of people newly infected with hepatitis C virus, the infection does not show any symptoms. In the remaining quarter of people, symptoms appear six to nine weeks (at most up to six months) after infection. These symptoms may take the form of loss of appetite, abdominal pain, nausea and vomiting, fever and joint pain. In five to ten percent of infected people, jaundice also occurs. After six months, the infection clears without treatment in 20 to 30 percent of those infected. In the remainder, however, the infection does not clear spontaneously within six months, but runs a chronic course (the vi-



Symptom of hepatitis C: yellow discoloration of the sclera.

rus remains in the liver). People with chronic infection usually live for years without symptoms, but late complications may occur in the form of liver failure or hepatocellular carcinoma. In about one in three patients, the life-threatening stage of liver cirrhosis (hardening of the liver, “shrunken liver”) is reached after 20 years, with the concomitant risk of the portal vein to the liver rupturing.



Liver cirrhosis

To avoid these long-term consequences, patients are treated in an effort to cure the infection. Until 2013 the standard treatment for a cure consisted of the combined administration of a pegylated interferon with ribavirin, supplemented in the case of genotype 1 with a medicine from the class of hepatitis C protease inhibitors. The pegylated interferon, which are produced with the aid of gene technology and chemistry, are modeled on an endogenous transmitter substance that stimulates the immune system to combat the virus. The hepatitis C protease inhibitors, which have been available since 2010, block the enzyme hepatitis C protease, which the virus needs in order to multiply in liver cells. However, the success of treatment can vary widely, depending on the hepatitis C variants present, which are described as genotypes on the basis of their genetic differences. In Europe, genotypes 1, 2 and 3 are the most widespread, type 1 accounting for about 70 percent of

cases. It is precisely this genotype that proved more difficult to combat than the two others. Nevertheless, these treatments were a huge step forward: whereas the cure rate just 20 years before stood at 1 percent, these combination treatments produced a cure in around 80 percent of patients infected with hepatitis C genotype 2 or 3; while in the case of infection with genotype 1 the cure rate stood at 75 percent. However, many patients treated with both pegylated interferon and ribavirin showed marked side effects such as fever and chills (pegylated interferon) and anemia (ribavirin). And the treatments lasted many months.

Virus inhibitors as new approach

The duration of treatment has fallen from six months to six to twelve weeks as a rule thanks to new medicines – with markedly fewer side effects and the prospects for a cure at well over 90 percent and even close to 100 percent. This also allows patients to dispense with interferon, which is problematic because of its side effects. The new class of antiviral agents selectively block a specific virus protein, protease, which the hepatitis pathogen needs in order to replicate in the body. This new generation of direct virus inhibitors knocks out the “copying machine” of the hepatitis C virus. Some of the new products inhibit the protease enzyme and thus prevent the proper cleavage of these newly produced viral particles. Others suppress the polymerase enzyme, which is responsible for the assembly of the viral genetic molecules.

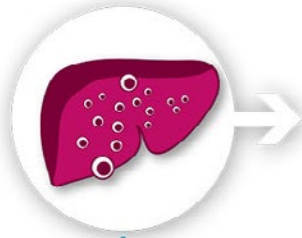
Most of these new antiviral inhibitors have been launched onto the market in the last two years. Experts speak of a gigantic breakthrough, because the products and the combination of them have proved outstandingly safe and are generally well tolerated by patients. In terms of efficacy and tolerability they eclipse all previous treatments. A disadvantage is their high price, which has caused more of a public stir than the exceptional / or very remarkable medical advance they represent. Besides the high treatment costs it is not least also the possibility of suddenly being able to cure all patients diagnosed with hepatitis C that sees health insurers confronted with financial limits.

Vaccination: new hope

To prevent hepatitis C even developing in the human

Course of hepatitis C infection showing the liver in various stages of the disease

Acute hepatitis C infection

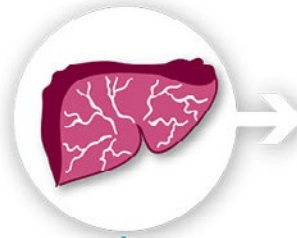


up to 6 months

70–80% of HCV infections become chronic

0 to 20 years

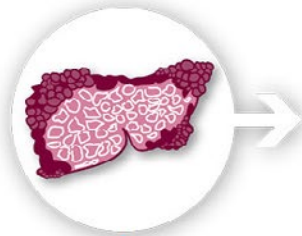
Chronic hepatitis C infection



20–30% of people with HCV infection develop liver cirrhosis/fibrosis

20 to 30 years

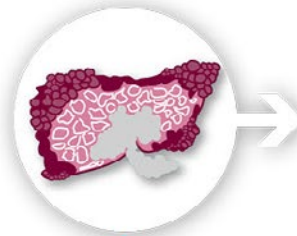
Liver cirrhosis/fibrosis



Hepatocellular carcinoma develops in 1–4% of people with HCV infection per year

from 30 years

Hepatocellular carcinoma



body in the first place, an international team of researchers is working on a vaccine. Physicians at the Cantonal Hospital of St. Gallen are also involved in this research. A first step towards a hepatitis C vaccine was to establish the origin of the virus. To this end, an international research team studied more than 4000 rodent species and almost 3000 species of bat from all five continents for pathogens related to the hepatitis C virus. And the scientists found what they were looking for: in rodents and bats. This is interesting because no animal reservoir is known for most human viruses, and it did not therefore seem necessarily obvious to look for hepatitis C or related viruses in animals.

After laboratory tests and animal experiments in the framework of the European PEACHI study under the leadership of the University of Oxford, the first person was recently vaccinated against hepatitis C in St. Gallen. Instead of antibodies, special killer cells are injected into the body. These seek out the infected liver cell and destroy it. The team from Oxford combined two different vaccines, which are administered at an interval of eight weeks. The first

vaccine, which is based on chimpanzee adenovirus (ChAd3) and expresses various HCV proteins, serves as a primer. This is intended to initiate an immune response, which is then reinforced by a booster. For the booster, the team uses a modified cowpox virus known as Modified Vaccinia Ankara (MVA), which likewise expresses HCV proteins. MVA is a highly attenuated virus, which was especially developed for use in vaccines. The researchers are also pinning their hopes on this vaccine technique in the fight against other viral diseases, such as malaria, HIV and even tuberculosis.

It would be ideal if we could understand the complicated mechanisms of a body without stressful animal experiment. Unfortunately that is not yet possible today. But the dilemma will remain for a long time to come: basic research without experiments in animals would mean abandoning any medical progress. Mice Times aims to explain why and therefore reports on medical success stories that were only possible thanks to animal experiments.

IMPRESSUM

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