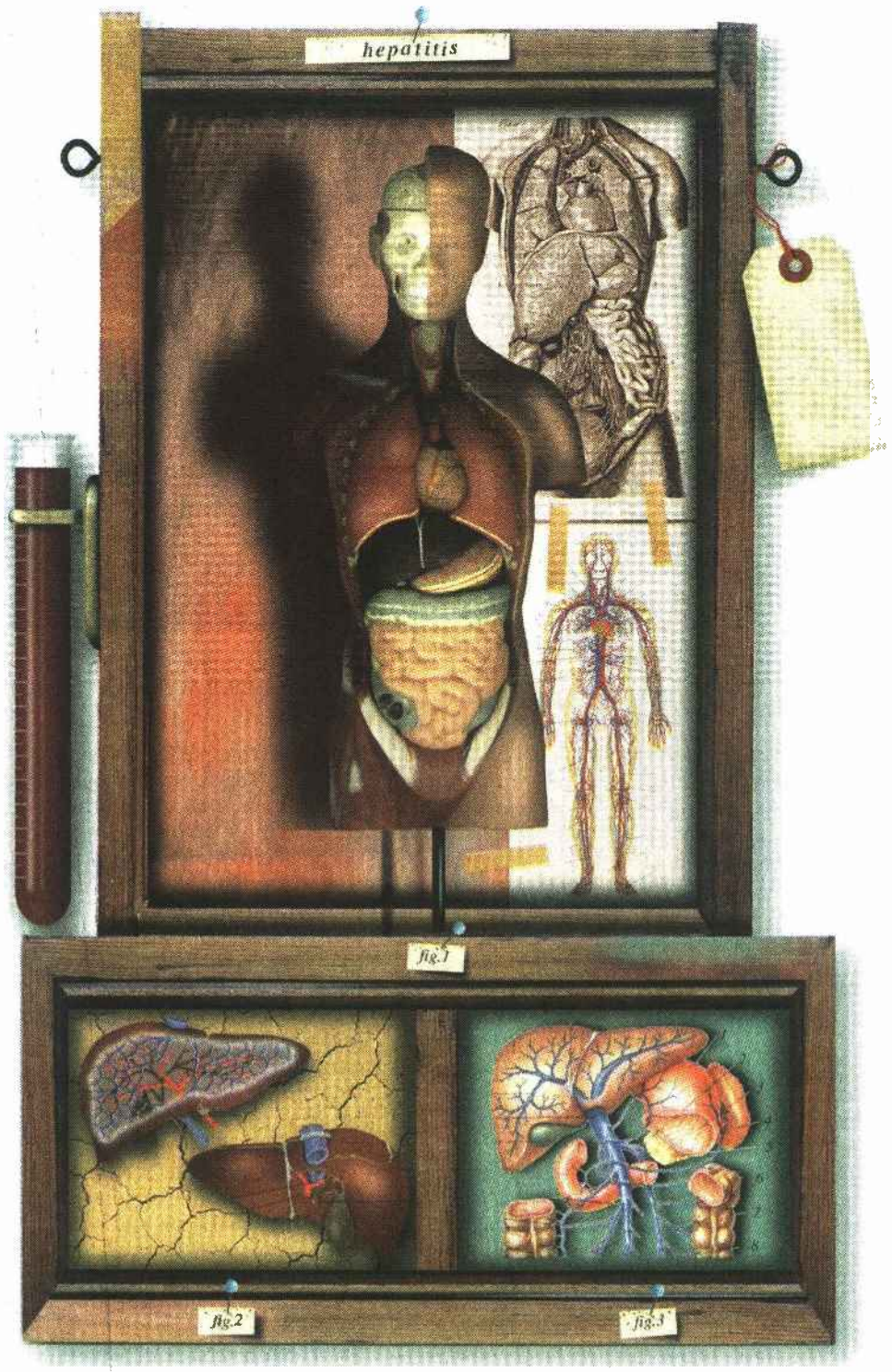
Living with liver disease – hepatitis C seems to be biting the dust

Three global pharmaceutical companies have separately come up with an oral pill – comprised of different molecules but of the same class of drugs – that nearly eliminate the virus called HCV from the blood of almost 100 percent of treated patients.

Judy Siegel-Itzkovich reports



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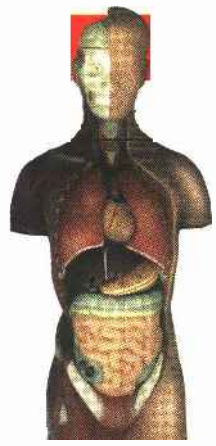

Hepatitis C
New drugs could wipe out the chronic liver infection

There is no cure yet for AIDS, but there is great hope that an experimental drug – based on findings about human immunodeficiency virus – will cure hepatitis C virus (HCV).

If the simultaneous breakthroughs by three pharmaceutical giants pan out, they will undoubtedly be hailed as the biggest news in pharmacology since penicillin. Some four million people around the world are infected with hepatitis C every year. In total around 170 million people are infected with the chronic liver infection, but many are unaware of it, and it kills some 350,000 to 500,000 annually.

Three experimental pills have been developed – all from the same class of drugs but involving different molecules.

One is the drug combination of ABT-450/ritonavir (150/100mg) co-formulated with ABT-267 (25mg), dosed once daily, and ABT-333 (250mg) with or without ribavirin. It was developed by the Chicago-based global pharmaceutical company AbbVie. The 25,000-employee company separated from Abbott Laboratories last year.

The second combination was developed by Bristol-Myers-Squibb and includes daclatsavir and asunaprevir. BMS is a pharmaceutical company headquartered in New York City. The Bristol-Myers part was established in 1887, but it merged with the Squibb Corporation in 1989.

The third is Merck, Sharp and Dohme's combination of MK-5172 and MK-8742. Known outside North America as MSD, the New Jersey-based company is one of the largest pharmaceutical firms in the world.

A few weeks ago, researchers from the companies presented the exciting and convincing results of their phase III hepatitis C development programs at a London conference on liver disease. The clinical studies showed that the oral, interferon-free regimens for the treatment of HCV infection in adults with the most common genotype 1 were very successful, causing the virus to disappear in patients' bodies.

They were tested in the past three years on thousands of patients in dozens of hospitals in numerous countries, including Israel. The sites of the clinical trials here included Jerusalem's Shaare Zedek Medical Center (SZMC), Rambam Medical Center in Haifa and Sheba Medical Center at Tel Hashomer.

The three drug combinations – given in pill form and dosed twice daily – have not yet been given commercial names. But the US Food and Drug Administration is due to approve them for marketing later this year, followed by licensing in Israel. Until then, they are available only as part of hospital trials.

"When the drugs are licensed, they will probably be expensive," said Dr. Yoav Lurie, the head of the liver disease unit in SZMC's gastroenterology branch, in an interview in his office with *The Jerusalem Post*, "and that is a conundrum health authorities all over the world are facing."

In the new formulations, the combination of multiple mechanisms of action has been found to interrupt the replication of HCV, and provides sustained virologic response rates across different patient populations.

"The new treatment is real news that is could wipe out the disease," Lurie said. "In our experience, there were few or no side effects from the drug combination."

Lurie came to the Jerusalem hospital a few years ago after working as director of the liver clinic at Kaplan Medical Center in Rehovot and head of the hepatitis clinic at Tel Aviv Sourasky Medical Center. The prevalence of hepatitis C in Israel is between one percent to 1.5% of the population.

THERE ARE five main hepatitis viruses – types A, B, C, D and E, he said. Hepatitis A used to be well known in day care centers due to transmission during diapering of toddlers without having washed hands thoroughly. But this problem has largely disappeared with the development of live attenuated and killed vaccines.

Hepatitis B can spread by sexual contact, the transfer of blood or serum through shared needles in drug abusers, accidental needle jabs with needles contaminated with infected blood, blood transfusions, kidney dialysis and "vertically" by infected mothers to their newborn babies. The infection also can be spread by tattooing, body piercing and sharing razors and toothbrushes (if there is contamination with infected blood). As many as 10% of patients with HBV develop chronic HBV infection and can infect others. Their condition can result even decades later in cirrhosis, liver failure and liver cancer. This too has gradually been eliminated in children by vaccines given to babies as part of the regular immunization schedule.

Hepatitis D virus, also known as the delta virus, is a small virus that requires simultaneous infection with HBV to survive and is essentially spread in the same ways at hepatitis B. HDV is not a concern in Israel. Hepatitis E virus is similar to hepatitis A and occurs mostly in Asia, where it is transmitted by contaminated water and unsafe food.

"Hepatitis E is sporadic. It was thought there was none in Israel, but a few dozen cases have been reported," said Lurie. "It can result in fatalities, especially when pregnant women are involved. Who knows? It could be the tip of an iceberg."

THAT LEAVES hepatitis C as the main problem. It was initially spread in the West, including Israel, by blood transfusions (as well as to hemophiliacs, whose necessary clotting factor was made from large amounts of plasma prior to the development of the safe recombi-

DR. YOAV LURIE and young collegues. (Judy Siegel Itzkovich)

nant form) before they started checking for the virus (and for HIV as well) in 1992. HCV is also spread by epidermic needles shared among drug abusers, kidney dialysis, needle jabs and piercings and tattoos performed with non-sterile needles. This form has been the most common cause for liver transplantation in the West.

Lurie reported eight years ago in the journal *Hepatology* that the spread of HCV due to piercing and tattooing was significantly lower in Israel than in other countries, but it seems that the risk is now higher among young people as a result of these practices at unsupervised establishments becoming much more common.

About half to 70% of patients with an acute infection develop chronic HCV, while the acute infection inexplicably disappears in many of the remainder. Those with chronic HCV infection are at risk for developing cirrhosis, liver failure and liver cancer, according to Lurie.

Other medical centers abroad that conducted clinical trials on the new drug treatment were Beth Israel Deaconess Medical Center in Boston and the University of Texas-San Antonio. The Massachusetts center recently reported in *The New England Journal of Medicine* that after giving the oral drug combination to patients over 12 weeks, an incredible 94% to 99% of patients were cured of hepatitis C. Results were similar in patients who had never been treated or who had previously received an injected combination of peginterferon and ribavirin, but these patients suffered from significant side effects.

Similar results were obtained at the University of Texas. The drugs wiped out the virus in 90% to 96% of cases and were well tolerated by these patients, said Dr. Fred Poordad, who also published his team's findings in the NEJM.

"These are out-of-the-ballpark response rates, not on the same planet as interferon," Poordad said. "The reason this study is so profound is because interferon is not tolerated, nor is it safe in many people with cirrhosis. Many of the patients with cirrhosis in this study were not even eligible to be treated with interferon."

A few weeks ago, the World Health Organization issued its first-ever guidance for the treatment of hepatitis C. The publication of the WHO guidelines for the screening, care and treatment of persons with hepatitis C infection was triggered by the development of effective and safer oral hepatitis medicines, along with the promise of even more new medicines in the next few years.

"The WHO recommendations are based on a thorough review of the best and latest scientific evidence," said Dr. Stefan Wiktor, who heads the organization's global hepatitis program. "The new guidance aims to help countries to improve treatment and care for hepatitis and thereby reduce deaths from liver cancer and cirrhosis."

The WHO said it will work with countries to introduce the guidelines as part of their national treatment programs, especially in the developing world.

"Hepatitis C treatment is currently unaffordable to most patients in need. The challenge now is to ensure that everyone who needs these drugs can access them," said Dr. Peter Beyer of the WHO's essential medicines and health products department. The new guidelines included approaches to increase the number of people screened for hepatitis C infection, advice as to how to mitigate liver damage for those who are infected and how to select and provide appropriate treatments for chronic hepatitis C infection.

"Many people remain unaware – sometimes for decades – that they are infected with hepatitis C," said Dr. Andrew Ball of the WHO's HIV/AIDS department, where the global hepatitis program is located. "Greater awareness on the risks associated with hepatitis C should lead to a demand for services and expansion of laboratory capacity and clinical services so that more people can be tested, treated and cured."

Help on the way for hepatitis C patients who also have kidney failure

Hepatitis C has been enough of a problem, but there are also a dozens of Israelis who also have kidney failure and undergo kidney dialysis as well. Dr. Yoav Lurie of the capital's Shaare Zedek Medical Center, along with liver experts at Sheba Medical Center at Tel Hashomer, Tel Aviv Sourasky Medical Center and Rambam Medical Center and Carmel Medical Center in Haifa are about to test the Merck drugs MK-5172 and MK-8742 on their kidney failure patients (or those who have undergone kidney transplants but the new organs do not function well enough) who also have hepatitis C.

"Such people are usually very fragile because of their multiple conditions and most of them have not been eligible for current medications because these could worsen their general and kidney conditions," said Lurie. "But with the development of the experimental new pills, we are about to test one of them and are in the process of reviewing possible candidates. We can accept only those who are in reasonable condition." The international trial will take up to six months, said Lurie, but "we are very hopeful, because in previous cases, no side effects were observed in patients with normal kidney functions." Potential recipients with both conditions are invited to contact him at yoav@szmc.org.il or liverunit@szmc.org.il or to call the unit at (02) 6555035. Those not near Jerusalem can go to the liver clinics at any of the other four medical centers. *J.S.-I.*