the damaged meniscus back to a stable rim”).
Without a sham comparison group, it is not possible to distinguish between a true treatment effect and nonspecific (placebo) effects that might arise from other factors, such as the patient’s expectation of benefit. In view of the expected bias favoring surgery, it is noteworthy that the primary analysis in this trial failed to show an advantage of surgery. Similarly, without a sham surgical comparison group and a blinded outcome assessment, it is not possible to draw firm conclusions regarding the benefits of surgery in the 30% of patients randomly assigned to physical therapy who had improvement after crossover.

Potential risks must be considered in assessing the comparative effectiveness of surgery and nonoperative interventions. Known perioperative risks of arthroscopy include thrombosis, infection, and anesthesia-related complications. There is also a concern that people who undergo this procedure may have an increased risk of progression of osteoarthritis and an increased likelihood of joint replacement.\(^9,10\) Katz et al. reported no between-group differences in adverse events over the first 12 months of their trial, although no data were presented on when adverse events occurred in relation to surgery or physical therapy. Further follow-up is planned, but this study may not have adequate power to assess differential risks in long-term outcomes.

Currently, millions of people are being exposed to potential risks associated with a treatment that may or may not offer specific benefit, and the costs are substantial. The results of the present trial by Katz and colleagues, together with prior data, suggest that surgery is not routinely needed for presumed symptomatic meniscal tears in patients with knee osteoarthritis and that physical therapy may be appropriate initial management, although the efficacy and cost-effectiveness of physical therapy also need to be confirmed in high-quality trials. These results should change practice. They should also lead to reflection on the need for levels of high-quality evidence of the efficacy and safety of surgical procedures similar to those currently expected for nonoperative therapy.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Monash Department of Clinical Epidemiology, Cabrini Hospital, Malvern, and the Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne — both in Victoria, Australia.

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Micromanaging Hepatitis C Virus

Judy Lieberman, M.D., Ph.D., and Peter Sarnow, Ph.D.

Hepatitis C virus (HCV), a positive-stranded RNA flavivirus, persistently infects approximately 170 million persons worldwide and can lead to cirrhosis and hepatocellular carcinoma. The approval of two HCV protease inhibitors, telaprevir and boceprevir, by the Food and Drug Administration (FDA) in 2011 dramatically improved therapy. These drugs are used in combination
with pegylated interferon alfa and ribavirin. Although protease inhibitors have greatly enhanced the sustained viral response rate, these inhibitors are active against only the dominant viral genotype found in North America and Europe (genotype 1), and about a third of patients with genotype 1 infection do not have sustained viral repression. Without concurrent administration of interferon and ribavirin, drug resistance develops rapidly. Moreover, the use of interferon is associated with substantial side effects in many patients, and prolonged treatment (≥24 weeks) with these drugs is required to eliminate the virus, after which some patients still have a relapse. The protease inhibitors have nontrivial side effects and interfere with the cytochrome P-450 system, leading to drug–drug interactions.

To address these problems, second-generation protease inhibitors and small-molecule drugs to inhibit other viral enzymes are being evaluated in clinical studies. In the future, drug cocktails that target multiple HCV enzymes simultaneously may overcome the problems of monotherapy, as they have for infection with the human immunodeficiency virus. However, new therapeutic approaches that are less likely to create resistance and are effective against the diverse strains of HCV would be a welcome addition to the drug arsenal.

Janssen et al. now describe in the Journal just such an approach. This strategy arose from the discovery that to survive and replicate in liver cells, HCV depends on the most abundant host liver microRNA, miR-122. MicroRNAs consist of approximately 22-nucleotide RNAs that suppress the expression of messenger RNAs bearing partially complementary sequences by accelerating their degradation and inhibiting their translation into protein. The liver-expressed miR-122 binds to two highly conserved sites in HCV RNA, but rather than causing it to be degraded, miR-122 protects it from degradation. All tested strains of HCV depend on miR-122, suggesting that it is a universal HCV Achilles’ heel.

The action of a microRNA can be antagonized by introducing small RNAs with a complementary sequence, called antisense oligonucleotides, into cells. However, getting nucleic acids across the cell membrane into the cytosol, where the virus replicates, in vivo and in sufficient amounts for activity without unacceptable toxicity has been challenging. Because the liver is designed to remove toxic substances from the body, the hurdle for nucleic acid delivery to that organ is lowest. In fact, after two decades of research to convert antisense oligonucleotides into useful drugs, the first such drug, mipomersen, which inhibits the expression of apolipoprotein B-100 in the liver, was approved by the FDA to treat familial hypercholesterolemia.

In the study by Janssen et al., the investigators used a chemically modified antisense oligonucleotide, which has an enhanced binding affinity, is resistant to nucleases, and is able to penetrate cell membranes. As a consequence, miravirsen, the miR-122 antisense oligonucleotide that they tested, enters liver cells and binds tightly and stably to miR-122, preventing the latter from binding to HCV RNA. A preclinical study in two HCV-infected chimpanzees had shown that miravirsen (at a dose of 5 mg per kilogram of body weight) given weekly for 12 weeks reduced viral load by approximately 2.6 logs without causing drug resistance or serious side effects.

In the phase 2a dose-finding study, Janssen et al. administered subcutaneous weekly doses of miravirsen (3, 5, or 7 mg per kilogram) or placebo for 5 weeks in patients who had not undergone previous therapy for HCV infection. The patients did not receive any interferon or ribavirin but were allowed to add this combination therapy 2 weeks after the last miravirsen treatment in the lowest-dose group and 5 weeks after miravirsen in the higher-dose groups. Miravirsen treatment caused no significant toxic effects, aside from mild injection-site reactions and a transient slight increase in serum liver enzymes, and led to a dose-dependent reduction in viral load. At the highest dose, the viral load declined by approximately 3 logs and was below the level of detection in four of nine patients. There was no sign of drug resistance, as verified by sequencing of the targeted viral sequence. However, after miravirsen was stopped, levels of virus rebounded in patients who had not begun receiving interferon and ribavirin. Since miR-122 normally controls cholesterol levels independently of its effect on HCV, patients receiving miravirsen had a sustained decrease in serum cholesterol levels.
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From the Program in Cellular and Molecular Medicine, Boston Children’s Hospital, and the Department of Pediatrics, Harvard Medical School — both in Boston (J.L.) — and the Department of Microbiology and Immunology, Stanford University, Palo Alto, CA (P.S.).

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