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THERAPEUTICS

New drugs hit the target

With two recently approved drugs and dozens more in the pipeline, hepatitis C treatment will improve over the next decade.

BY JANA SCHLÜTTER

When Charles Gore talks about some of his colleagues, there is more than a hint of urgency in his voice. Although he cleared his hepatitis C virus (HCV) infection after receiving the standard treatment, two of his staff at the World Hepatitis Alliance, an advocacy organization, recently had liver transplants. "And they are lucky," says Gore, who is president of the alliance. "This treatment does not help about 50% of the patients who are infected with the most common form of the virus. So their liver becomes worse, and many of them cannot get a transplant. They are facing death."

Around the globe, patients who have not been cured by the current treatment, a combination of interferon-α and ribavirin, are waiting for new drugs. So far, their doctors have had nothing to offer them but another 48-week-round of the same drug combination, which had its last upgrade in 2001 when researchers attached a molecule called polyethylene glycol to interferon-α. This 'pegylation' allows interferon-α to stay in the body much longer, reducing the frequency of injections from three per week to one. But the side effects are just as harsh, including flu-like symptoms, anaemia and depression. And although the patient being treated may be too weak to work or enjoy family life, the virus often manages to survive and prosper under these conditions. At most, 20% of patients are cured by this second course of treatment. Still, there was no alternative.

This situation is about to change. Two powerful weapons against chronic HCV infection have been licensed: the protease inhibitors telaprevir, from Vertex Pharmaceuticals, based in Cambridge, Massachusetts, and boceprevir, from drug company Merck, headquartered in Whitehouse Station, New Jersey. When either drug is added to the current therapy, the cure rate increases for patients who have so far been spared the daunting year-long treatment: that is, 'treatment-naive' patients. The drugs also offer hope to those increasingly desperate patients who have not been helped by the standard treatment: instead of around a 20% chance of a cure, these 'treatment-experienced' patients now have a 30–90% chance. "We are approaching a new era of management of this disease," says Mark Thursz, a hepatologist at Imperial College London and current secretary-general of the European Association for the Study of the Liver (EASL).

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The drug manufacturers have tailored these protease inhibitors to HCV genotype 1, one of at least six forms of HCV. Genotype 1 is particularly widespread in the United States and Europe and is one of the least responsive to the standard treatment. The clinical studies coming out now, Thursz says, "show that the new drugs can tame the pit bull terriers of the hepatitis C world: the genotype 1 viruses."

In addition to telaprevir and boceprevir, there are dozens of compounds in the pipeline, and that's only counting the ones that drug manufacturers are willing to disclose. These drugs target many aspects of the virus's life cycle — the stages it goes through in the liver cell to reproduce itself. Used in combination, the new agents might be able to target all HCV genotypes at once, while improving the cure rate and preventing drug resistance from emerging. Although most of these drug candidates are being added to the current treatment, an interferon-free regimen has recently shown promise — a possibility that could substantially reduce treatment side effects and increase adherence.

DIRECT HITS

In the current regimen, interferon-α boosts the patient's immune system, and ribavirin is a general inhibitor of virus replication. By contrast, the new drugs target HCV directly. Telaprevir and boceprevir block HCV's NS3/4A protease. After an HCV particle attaches to and enters a liver cell, it releases its RNA, which is subsequently translated into a single polyprotein (see 'The life of HCV'). This long chain is cleaved into functional proteins by NS3/4A, which acts like a pair of molecular scissors. Without the protease, functional viral enzymes and structural proteins are not generated, so HCV cannot complete its life cycle.

This March, the drug companies reported results of phase III clinical trials of telaprevir and boceprevir, each coupled with the current therapy, at EASL's International Liver Congress in Berlin. Two-thirds to three-quarters of treatment-naive patients with HCV genotype 1 are likely to clear the virus permanently. And treatment time is expected to be halved for patients in this group who have undetectable levels of virus after four weeks of treatment.

More hotly anticipated were the data for the treatment-experienced patients, including relapsers, whose virus had become undetectable but rebounded after their previous treatment ended; partial responders, whose

viral load decreased by at least 99% but never became undetectable; and null responders, who previously had little success in fighting the virus. Telaprevir was tested in the Realize trial, which involved 662 patients from Europe and the United States. Adding telaprevir for 12 weeks to a 48-week-treatment course increased the cure rates from 24% to as high as 88% in relapsers, from 15% to 59% in partial responders, and from 5% to 33% in null responders. Boceprevir was tested in 403 patients in centres across the United States and Europe in the Respond-2 trial. Adding boceprevir for 32–44 weeks caused the cure rate to climb from 29% to 69-75% in relapsers and from 7% to 40-52% in partial responders. (Null-responders did not participate in this trial.)

"To have direct-acting antivirals against hepatitis C and to see such increases in cure rates is a huge step forward," says Stefan Zeuzem, a hepatologist at the Goethe University Medical Center in Frankfurt, Germany, who was involved in both the Realize and Respond-2 trials. But these drugs are not cheap. "Cost will be a major issue," he says. "However, we are preventing liver cancer and other end-stage liver diseases, which makes it worthwhile. We are aiming for a cure, not just a few more weeks to live."

Both of these drugs also have side effects. More than half of the patients treated with telaprevir developed a rash, with 3–6% having a rash severe enough to halt treatment. Boceprevir is associated with anaemia (similarly to telaprevir) and can cause a metallic taste in the mouth, both of which affect nearly half of all patients. These problems are in addition to those caused by interferon-α and ribavirin, meaning that nearly every patient in the clinical trials suffered from at least one side effect. "It's still a tough treatment," says Gore. "For patients, it's very important that clinicians manage these side effects well."

If side effects cause patients to abandon treatment on the new regimen, this could lead to HCV developing resistance to the new drugs. The new protease inhibitors cannot be given alone and must be given with interferon-α and ribavirin to prevent protease-inhibitor resistance emerging. Thursz adds that as boceprevir and telaprevir are similar compounds, resistance to one will probably translate into resistance to the other (so-called cross-resistance), restricting future treatment options.

"The new drugs can tame the pit bull terriers of the hepatitis C world: the genotype 1 viruses."

HCV is a highly mutation-prone virus, with many genetic variants present in any one host. Before treatment starts, variants that are resistant to a particular drug make up a minority of the viral population. Under selective pressure of the antivirals, however, these variants could become the dominant strains. "We understand resistance and have to manage it," says Jean-Michel Pawlotsky, a hepatitis specialist at the University of East Paris in Créteil, France, and director of the French National Reference Center for Viral Hepatitis B, C and delta. He recommends that these new drugs should be administered at expert centres that can monitor resistance issues: "It is better to be well-treated than just treated," he says.

Despite the high cure rates, not every HCV-infected patient will benefit from the new drugs. Possible drug–drug interactions are not yet fully understood. And there are no data for the many patients who are co-infected with HIV or for patients with end-stage renal disease, decompensated (or extremely advanced) liver cirrhosis or a recent liver transplant. Furthermore, telaprevir and boceprevir have been licensed by the US Food and Drug Administration only for treating HCV genotype 1 infection. As Pawlotsky says, "What we are seeing now is just the first step into the era of direct-acting antivirals. It will cause a real shift, but it's not a full revolution."

COVERING EVERY ANGLE

More than 50 other drugs are, however, in the research and development pipeline (see 'Drug candidates for treating HCV infection 2011'). Many of these are in new classes — that is, they target different mechanisms — and can be combined to create antiviral cocktails, limiting the emergence of drug resistance. With so many new agents snapping at their heels, boceprevir and telaprevir might have a very limited time as the dominant new drugs, says Zeuzem.

Two other first-generation protease inhibitors are in phase III trials: TMC435, from Tibotec Pharmaceuticals, in Beerse, Belgium, and pharmaceutical company Medivir in Huddinge, Sweden; and BI201335, from pharmaceutical company Boehringer Ingelheim, headquartered in Ingelheim am Rhein, Germany. Both are taken once daily instead of three times, seem to cause fewer side effects and might even be more potent than boceprevir and telaprevir.

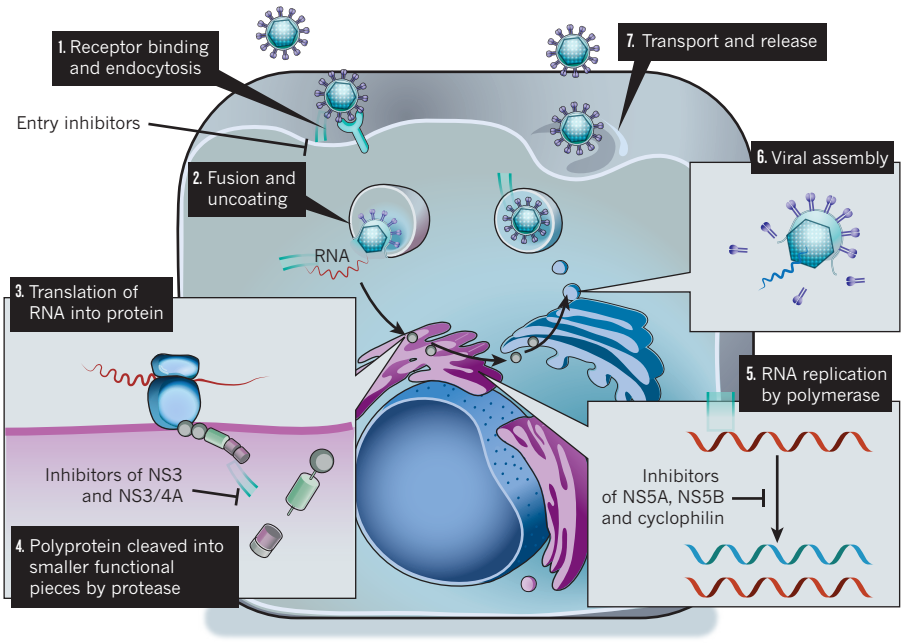
The second generation of protease inhibitors is expected to be led by Merck's MK-5172, a compound that does not seem to have cross-resistance issues with other drugs of this class and might be effective across multiple genotypes. "We want to see if the resistance profile is robust enough that we can treat people who are failures from earlier generations of protease inhibitors," says Keith Gottesdiener, vice president for hepatitis C clinical development at Merck. "That would be exciting if it was proven in the clinic."

The pharmaceutical company F. Hoffmann-La Roche, headquartered in Basel, is about to start phase III trials of mericitabine, which blocks the activity of HCV's polymerase enzyme, NS5B. By mimicking the building blocks of RNA, mericitabine is incorporated into newly formed viral RNA but prematurely terminates it, halting the life cycle.

Another protein generating immense interest as a drug target is NS5A. Its precise function is mysterious, but it seems to be involved in the replication, assembly and release of HCV.

THE LIFE OF HCV

Once it has infected liver cells, HCV goes through discrete stages of replication that are targeted by drugs in development.



SOURCE: CIESEK, S. & MANNS, M. P. NAT. REV. GASTROENTEROL. HEPATOL. 8, 69–71 (2011).

DRUG CANDIDATES FOR TREATING HCV INFECTION 2011
A sample of some of the novel agents in development to target HCV

Mechanism	Direct-acting antiviral agents				Host-targeting agents			
	Inhibitor of polyprotein processing	Inhibitor of HCV replication			Anti-apoptotic agent	Antiviral agent	Immunomodulatory agent	Inhibitor of virus fusion with host cell
Target	NS3 or NS3/NS4A protease	NS5A	NS5B polymerase		Caspases	Cyclophilins	Interferons	Viral entry
			Nucleoside analogue	Non-nucleoside inhibitor				
Recently approved	Telaprevir (Vertex) Boceprevir (Merck)	None	None	None	None	None	None	None
Phase III	TMC435 (Tibotec and Medivir) BI201335 (Boehringer Ingelheim)	None	None	None	None	Alisporivir (DEB025; Novartis)	None	None
Phase II	ACH-1625 (Achillion) BMS-650032 (Bristol-Myers Squibb) BMS-791325 (Bristol-Myers Squibb) Danoprevir (RG7227; Roche) GS-9256 (Gilead) GS-9451 (Gilead) ABT-450/r (Abbott and Enanta) Vaniprevir (MK-7009; Merck)	ABT-267 (Abbott) BMS-790052 (Bristol-Myers Squibb) GS-5885 (Gilead)	IDX184 (Idenix) Mericitabine (RG7128; Roche) PSI-7977 and PSI-7851 (Pharmasset) RG7128 (Roche and Pharmasset)	ABT-333 (Abbott) ABT-072 (Abbott) ANA598 (Anadys) BI207127 (Boehringer Ingelheim) Filibuvir (Pfizer) IDX375 (Idenix) Tegobuvir (GS-9190; Gilead) VCH-916 (Vertex) VX-222 (Vertex)	IDN-6556 (Idun/Conatus)	NIM811 (Novartis) SCY-635 (Scynexis)	PEGylated interferon-λ (Bristol-Myers Squibb)	None
Phase I	GSK2336805 (GlaxoSmithKline) IDX320 (Idenix) MK-5172 (Merck) VX-985 (Vertex)	AZD7295 (AstraZeneca) PPI-461 (Presidio)	GS-6620 (Gilead) INX-08189 (Inhibitex) PSI-938 (Pharmasset)	GSK2485852 (GlaxoSmithKline) VX-759 (VCH-759; Vertex) GS-9669 (Gilead)	None	None	GS-9620 (Gilead)	ITX-5061 (iTherX)
Preclinical	ACH-1095 (Achillion) ACH-2684 (Achillion) AVL-192 (Avila) GNS-227 (GenoScience Pharma)	ACH-2928 (Achillion) BMS-766 (Bristol-Myers Squibb) EDP-239 (Enanta) IDX380 and IDX719 (Idenix) PPI-437, PPI-668, PPI-833 and PPI-1301 (Presidio)	PSI-661 (Pharmasset)	BILB 1941 (Boehringer Ingelheim)	None	None	None	ITX4520 (iTherX) PRO 206 (discontinued; Progenics) REP 9C (REPLICor) SP-30 (Samaritan)

BMS-790052, from biopharmaceutical company Bristol-Myers Squibb, headquartered in New York, was the first inhibitor in this class and is now in phase II trials. The pipeline is rapidly filling with others.

Cyclophilin A inhibitors block a host protein that is essential for viral replication. Candidates include alisporivir (DEB025), from drug company Novartis, headquartered in Basel, Switzerland, which is in phase III trials. In theory, targeting a human protein that HCV needs will render the virus' genotype or mutation status irrelevant and make it much less likely that resistant strains of HCV will emerge.

FREE FROM INTERFERON

There is also hope for patients who are not responsive to — or cannot tolerate — the backbone of triple therapy: interferon. This April at the International Liver Congress, Anna Lok, a hepatologist at the University of Michigan in Ann Arbor, presented data from a small phase IIa study of an interferon-free regimen in null responders. The study comprised patients on double therapy consisting of two classes of direct-acting antiviral: Bristol-Myers Squibb's BMS-650032 (a protease inhibitor) and BMS-790052 (an NS5A inhibitor). These patients were compared with a cohort taking quadruple therapy, consisting of these two antivirals plus interferon-α and ribavirin. The quadruple therapy suppressed HCV in 10 out of 10 patients for at least 12 weeks after treatment, whereas the interferon-free double therapy suppressed HCV in 4 out of 11 patients, with 6 being null or partial responders.

The numbers might not seem great, but they are a start. "The potential for an interferon-free regimen is some of the most exciting news this year," says Thursz. Without interferon-α and ribavirin, the virus was expected to rebound after treatment, but this occurred in only one case. "There is still a lot of work to be done. But this was a group of very difficult-to-treat patients with excellent outcomes. Although the numbers are small, I think this is the direction we can expect to go in the future."

Indeed, this possibility has energized hepatitis C researchers. "People would have laughed at you if you suggested something like this five years ago," says Zeuzem. "Now, we know that such a therapy might be available in another five to ten years."

Many of the other drugs in the pipeline, such as the NS5B inhibitors, could also be candidates for an interferon-free regimen, says Paul Pockros, co-director of clinical research at the Scripps Translational Science Institute in La Jolla, California, who is involved in phase II studies of mericitabine. Although mericitabine is slightly less effective than the protease inhibitors, it seems to be a safe drug with a high barrier to resistance. "This one would be a good partner for a protease inhibitor," says Pockros.

With all the excitement about new drugs, one would be forgiven for thinking that interferon has had its day. But there is also development on this front. Bristol-Myers Squibb has developed a variant called pegylated interferon-λ, which is designed to be more potent and safer than interferon-α. Interferon-λ docks with different receptors that are less common than the receptors for interferon-α. This interferon circumvents the bone marrow and therefore avoids anaemia and flu-like symptoms, so it might be a good partner for direct-acting antivirals. "This would help a lot of people who cannot tolerate the current interferon," says Zeuzem, who is involved in clinical trials of this drug.

With interferon-free regimens on the horizon, the question is whether a new interferon will be needed. But there are many potential pitfalls on the way to the clinic, and HCV is a very difficult virus to target. Researchers need as many options at their disposal as possible, says Zeuzem, "just in case."■

Jana Schlütter *is a freelance journalist based in Berlin.*