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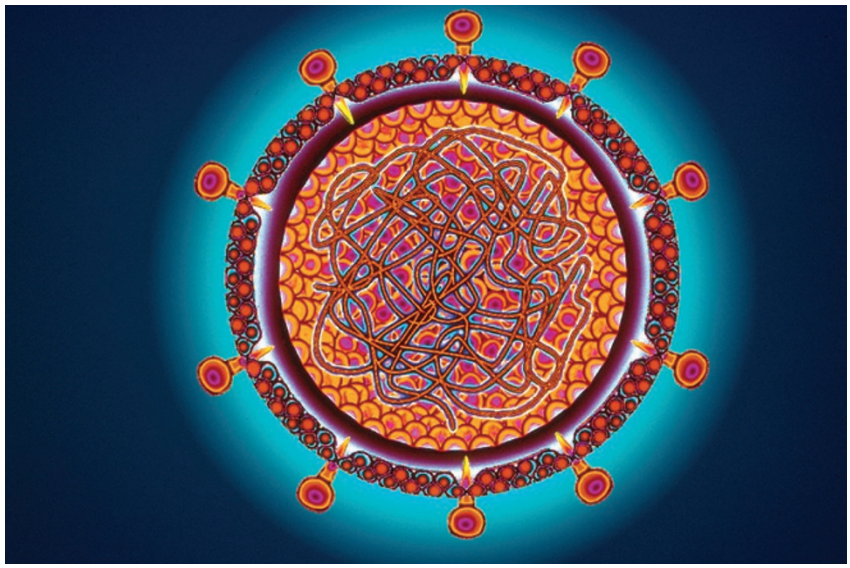
New Merck and Vertex drugs raise standard of care in hepatitis C



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Two new therapies to fight hepatitis C virus (shown as diagram) infections were approved by the US Food and Drug Administration in May.

The recent, near-simultaneous US Food and Drug Administration approvals of the viral protease inhibitors Victrelis (boceprevir) and Incivek (telaprevir) developed, respectively, by Merck and Vertex Pharmaceuticals, for treating hepatitis C virus (HCV) infection, represent genuine progress in an area poorly served by existing therapy. But these new therapies, approved in May, are not likely to remain in pole position for very long. Numerous other molecules in development based on various other mechanisms (**Table 1**) offer more tolerable alternatives. For those that make it to market, it will take some time to work out how best to deploy them in combinations tailored to different patient categories. "In HIV it took over ten years," says Frank Duff, vice president of virology development at Genentech, a subsidiary of Basel-based Roche. "I'd like to think there are some learnings that will allow that to happen more rapidly [in HCV]."

With Victrelis and Incivek, a new standard of care is emerging, in which one or the other of the two drugs will be added to the current treatment, which consists of a recombinant, pegylated version of the endogenous cytokine interferon-alpha (IFN-α) combined with the broad-spectrum antiviral drug Peg/Riba (ribavirin). Although the outcomes differ across different patient categories, the new triple regimens substantially improve the cure rates obtained with Peg/Riba alone.

HCV, a positive-stranded RNA virus belonging to the Flaviviridae family, is virologically distinct from other viruses that cause hepatitis or liver inflammation, such as hepatitis A virus (a Picornavirus) or hepatitis B virus (HBV; a hepadnavirus). HCV, which is usually spread by contact with infected blood, can also lead to liver cirrhosis, fibrosis and cancer, and it is a leading cause of liver transplant. It has been classified into 11 major genotypes, three of which have global distribution, according to the Geneva-based World Health Organization. This heterogeneity has hindered vaccine development efforts, whereas drug therapy offers more promise. "A cure is possible," says Eliav Barr, vice president, infectious diseases project leadership and management, at Merck, which gained ownership of Victrelis after its acquisition of Schering-Plough, of Kenilworth, New Jersey, in 2009. This is because HCV, unlike HIV or HBV, does not integrate into the host genome, so chronically infected individuals who respond to drug therapy can expect to clear the virus completely.

Merck, of Whitehouse Station, New Jersey, and Cambridge, Massachusetts–based Vertex has each gained approval for treating HCV genotype 1 infection, which accounts for ~60% of the estimated 170 million infections worldwide. It is the most prevalent genotype in the wealthy markets of North America, Europe and Japan. Genotype 1 infections are more severe and are less responsive to Peg/Riba therapy than either type 2 or 3 infections. Current Peg/Riba regimens lead to a cure—or, in virology parlance, sustained virologic response (SVR)—in ~40% of patients with type 1 infection. However, the treatment is associated with severe side effects, including anemia, depression and flu-like symptoms, which can cause some patients to discontinue therapy or to avoid starting it in the first place.

Incivek, in combination with Peg/Riba, appears to offer greater efficacy, achieving cure rates of 79–86% compared with 63–66% for people on Victrelis-based triple therapy. But the newly approved drugs also have major shortcomings, adding an extra safety and toxicity burden to a treatment that is already difficult to take. Victrelis requires a complicated dosing regimen and also increases the risk of anemia and of neutropenia that can be of life-threatening severity. Treatment with Vertex's Incivek, though shorter than its competitor's, is associated with increased incidence of severe rash, anemia and pruritus. Merck claims that of the two, its drug is safer. "Discontinuation due to anemia was higher with [Incivek] telaprevir. The need for transfusions was higher with [Incivek] telaprevir," says Barr. "Between the two, there's no question—Victrelis is the safer product." However, neither firm is contemplating a head-to-head study that would permit a direct comparison of the two drugs.

Dosing is another issue, as each drug needs to be taken three times daily. For instance, Roche is looking to use the generic HIV protease inhibitor ritonavir (originally Abbott's Norvir), which is metabolized primarily by cytochrome P450 3A (CYP3A), to improve bioavailability and allow lower dosing of its HCV protease inhibitor danoprevir, which is metabolized by the

Table 1 Selected HCV drugs in development

Company	Molecule	Mechanism	Stage
Merck	Victrelis (boceprevir)	NS3/4A protease inhibitor	Approved
Vertex, Johnson & Johnson (J&J)	Incivek (telaprevir)	NS3/4A protease inhibitor	Approved
Boehringer Ingelheim	BI 201335	NS3/4A protease inhibitor	Phase 3
	BI 207127	NS5B RNA-dependent polymerase inhibitor	Phase 2
Medivir, J&J	TMC435	NS3/4A protease inhibitor	Phase 3
Anadys Pharmaceuticals (San Diego)	Setrobuvir	Nonnucleoside inhibitor of NS5B RNA-dependent polymerase	Phase 2b
Biolex Therapeutics (Pittsboro, North Carolina)	Locteron	Controlled-release formulation of IFN-α2b	Phase 2b
Pharmasset, Roche	RG7128	Prodrug of cytidine nucleoside mericitabine polymerase inhibitor PSI-6130	Phase 2b
Pharmasset	PSI-7977	Pyrimidine nucleotide polymerase inhibitor	Phase 2b
	PSI-938	Guanine nucleotide polymerase inhibitor	Phase 1
Bristol-Myers Squibb	PEG-IFN-λ	Type III IFN with greater tissue selectivity than IFN-α	Phase 2b
	BMS-790052	NS5A replication complex inhibitor	Phase 2
	BMS-650032	NS3/4A protease inhibitor	Phase 2
Abbott, Enanta (Watertown, Massachusetts)	ABT-450/r	Protease inhibitor plus low-dose ritonavir	Phase 2
Peregrine Pharmaceuticals	Bavituximab	Targets phosphatidylserine exposed on surface of infected cells	Phase 2
Roche[a]	Danoprevir	NS3/4A serine protease inhibitor	Phase 2
Santaris Pharma (Horsholm, Denmark)	Miravirsen (SPC3649)	Locked nucleic acid (DNA phosphorothioate oligonucleotides flanked at each end by 2–4 oligos modified with an extra methylene bridge that fixes the ribose moiety in the C3′-endo sugar conformation) against miR-122–mediated HCV replication	Phase 2a
iTherX (San Diego)	ITX-5061	HCV entry inhibitor	Phase 1b

[a]Roche paid Intermune (Brisbane, California) $175 million to acquire all rights to danoprevir in October 2010.

same pathway. German company Boehringer Ingelheim of Ingelheim, Germany, and Medivir, of Huddinge, Sweden, are both developing once-daily low-dose inhibitors. Medivir is also touting the impact of its drug, TMC435, on 'null responders' or patients who have had no prior response to Peg/Riba therapy. The company recently reported four-week SVR data from a phase 2b trial, in which 57% of such patients cleared the virus. In comparison, only 29–32% of null responders receiving Incivek achieved a cure, and Merck did not include any such patients in its phase 3 program for Victrelis.

Medivir has a development alliance with Johnson & Johnson (J&J) of New Brunswick, New Jersey, which adds some spice to the competitive mix, as J&J also holds commercial and development rights to Incivek in Europe and several other territories. "I think they [J&J] clearly understand where the future lies—and that's clearly with TMC435," says Medivir CEO Ron Long. J&J is a little more circumspect. "Commercial strategy is proprietary," says a company spokeswoman. "Obviously we recognize that there are two partners involved, and therefore that needs to be looked at."

Eliminating IFN-α altogether from triple treatments is another major theme. "It is quite a toxic treatment, and people suffer under that drug," says Philip Thorpe, professor of pharmacology at the University of Texas Southwestern Medical Center, in Dallas, who is also scientific founder of Tustin, California–based Peregrine Pharmaceuticals. Peregrine is trying to dispense with IFN-α by subverting a mechanism that enables viruses to evade the immune response. The company uses bavituximab, a humanized monoclonal antibody that targets phosphatidylserine, an immunosuppressive phospholipid found on the interior of mammalian cell membranes, whose normal function is to allow apoptosis to proceed without provoking an immune response. Phosphatidylserine is 'flipped' to the exterior of cells that become virally infected, however, and it is also embedded on the surface envelopes of budding viruses. When thus exposed it exerts an immunosuppressive effect. "We're hoping that if we break the apoptotic mimicry of the HCV, we'll enhance its immunogenicity."

New York–based Bristol-Myers Squibb (BMS) is taking a more direct approach. It gained a PegIFN-λ development program when it acquired erstwhile partner Seattle-based ZymoGenetics in 2010. PegIFN-λ, a type III IFN, has a narrower activity profile than IFN-α as receptors for the cytokine are found on a more limited range of tissues, but it is active in the liver, the key organ affected by HCV. Recent phase 2b data are promising. "We were very confident the drug was going to differentiate on safety," says Doug Manion, vice president of global clinical development at BMS. "It turned out that it might also be more potent than IFN-α." BMS is also working on a first-in-class drug, BMS-790052, which inhibits an as-yet-unidentified component of the HCV replication complex. So far, it has demonstrated levels of efficacy equivalent to the most potent protease inhibitors. When combined recently in a 'quad' regimen, which also included the protease inhibitor BMS-650032 and Peg/Riba, it exhibited a dramatic effect on null responders. All 11 patients in the treatment arm of a small-scale trial attained a cure. "No one has ever achieved response rates like that in null responders," Manion says.

Elsewhere, Princeton, New Jersey–based Pharmasset's share price has climbed sharply this year on the strength of its pipeline of viral polymerase inhibitors, which Roche and other firms are testing in multiple combinations, including IFN-free regimens with and without ribavirin. Vertex recently gained a foothold in this drug class by entering an alliance with Alios BioPharma, of S. San Francisco, California. Merck and Roche will also jointly conduct combination trials of protease and polymerase inhibitors under an alliance announced in May.

As with any emerging new drug market, the range of options available to patients will widen in the coming years. For now, the big advantage Vertex and Merck hold over their rivals is their lead. Doctors—in wealthy countries at least—will have built up considerable clinical experience with Victrelis and Incivek before other drugs gain approval. Nevertheless, their reign as standard of care for treating HCV infection is likely to be considerably shorter than the decade enjoyed by the existing Peg/Riba treatment.

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