Evaluate Vantage

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Vantage Point – Need for safer hep C interferons spurring more research

The treatment of hepatitis C is expected to improve radically when a new class of direct-acting antiviral drugs – protease inhibitors such as telaprevir – reach the market, as early as this year. For the time being this new crop of products will still need the current standard of care, interferon and ribavarin, in the passenger seat.

So while mega-blockbuster potential is predicted for this new wave of therapies, demand is also set to remain high for interferons. With their side effect profile a major limiting factor, many companies are striving to keep up with advances elsewhere in hep C research and come with better and safer versions. Bristol-Myers Squibb spent $735m on ZymoGenetics last year largely for its interferon-lambda, while companies including Biolex Therapeutics and Polytherics are testing different approaches for new products. With a new crop of interferons slowly advancing, this represents another area to watch in the hep C field.

Good and bad news

Interferons – specifically interferon alpha is used for hep C - and ribavarin work by helping the body to fight the hep C virus (HCV) and in some cases can clear it completely. However this only happens in approximately half of patients so there is significant room for improvement – genotype-1 hep C is tougher to fight, genotypes 2 and 3 respond better, generally speaking.

Spearheaded by Vertex Pharmaceuticals' telaprevir and Merck & Co's boceprevir, these new protease inhibitors promise to radically improve response rates – studies suggest up to three-quarters of patients might be curable. But interferons remain an essential component of the new treatment regimen, and their tolerability issues a significant burden.

"If an interferon backbone is crucial for the management of hep C … it would be very helpful to have fewer side effects," says Dr Geoffrey Dusheiko, hepatologist at the Royal Free Hospital in London.

Flu-like symptoms are most common but depression, sight and digestion problems can also occur – sometimes so severe patients do not inject themselves as often as they should, or stop treatment altogether.

"The new first generation protease inhibitors can improve response rates in naïve patients to something like 70%, and in about two thirds of patients that was a shorter course of treatment. That's the good news.

"The bad news is that it is all on a backbone of interferon. There are numerous patients that have side effects, some patients have relative contraindications and some absolute contraindications to interferon. It's not an easy drug for patients to take," Dr Dusheiko says.

Approximately 10-15% patients cannot take interferon at all, Dr Dusheiko estimates, a number that may be higher in drug abusers or patients with psychological conditions. Considering there are thought to be approximately 130 million people worldwide infected with the virus, according to the UK's Hepatitis C Foundation, this is not a small number, he points out.

Interferon market

Despite significant tolerability issues interferons used to treat hep C generated more than $2bn in sales last year. Analysts expect demand to edge higher in the coming years, as hep C patients elect to try the new more effective anti-virals.

Pegylated interferons Pegasys and PEGIntron dominate the space, sold by Roche and Merck & Co respectively. Launched a decade ago, these products were a major advance because they cut the number of injections required from daily to weekly and significantly improved response rates.

The compounds are synthesised with a molecular tag called PEG (polyethylene glycol) attached, which prevents it being broken down in the body so quickly, sustaining effectiveness.

Various techniques are being employed to come up with new pegylated interferon alphas and in some cases new types of interferons altogether – improved tolerability being a major goal.

Peg alternative

One of the most advanced with a new interferon is North Carolina company Biolex, which is preparing for pivotal trials of its candidate, Locteron.

Using its platform technology Lex System, which genetically transforms the aquatic plant *Lemna* to produce biologic product candidates, the company has developed a controlled release version of interferon alpha 2b.

As a result, Locteron is dosed less frequently, every two weeks, and the 'burst effect' seen when current pegylated products are initially injected is eliminated, the company says.

"You get a nice even release of the drug over a two-week period," Dale Sander, Biolex's chief financial officer, tells *EP Vantage*. "In the early first 12 hours you get a much slower rise to Cmax [peak drug concentration in the body], which appears to eradicate a lot of the side effects."

Small mid-stage studies found Locteron superior to existing interferons on both efficacy and safety, with more than a 60% reduction in flu-symptoms.

This now needs to be repeated in much larger late-stage studies and Biolex is in talks with numerous potential partners, including big pharma, Mr Sander says. He hopes to strike a deal in the first half of this year, before pivotal studies begin.

Big backing

Evidence that new interferons are not just the realm of hopeful young biotechs came last year when Bristol-Myers bought ZymoGenetics, gaining full control of a product that it had licensed two years previously (*Bristol-Myers Squibb deals for new gentler and kinder interferon, September 8, 2010*).

Called PEG-interferon lambda, the molecule binds to a unique receptor with a more limited distribution throughout the body than the receptor for interferon alpha. The company hopes this will mean fewer side effects without compromising on efficacy.

A phase IIb study called Emerge is ongoing, seeking to recruit 600 patients, and could yield data in a couple of months time. Few financial analysts are attaching great hope to the product yet so these results will be read with interest – consensus data shows a launch in 2014 has been pencilled and sales of $87m by 2016, according to *EvaluatePharma*.

Tried and tested

The BMS product might be the most heavily-backed interferon in the pipeline but it still has much to prove. Biolex's Mr Sander points out that lambda does not have the decade's worth of supportive data that alpha has, and this could certainly make the regulatory pathway trickier.

New versions of pegylated interferon alpha would certainly have that advantage of familiarity, and several companies are working on this.

London-based Polytherics, for example, has developed a technique to place PEG in a different position.

"We attach the PEG so it's away from the business-end of the molecule," says Dr Ajay Mistry, Polytherics' business development manager. "We've engineered the interferon-alpha with a few histidine residues, attached the PEG to that region using our proprietary technology. What we get is an interferon-alpha that has the same half-life as [Pegasys], but is more active."

Pre-clinical data suggests the molecule's activity is eight-fold higher than existing products so the lower dosage required will mean less side effects and, ultimately, greater efficacy, Polytherics hopes.

The candidate, HiPEG-interferon-alpha-2a, has yet to be tested in humans and the company is seeking a partner to help take the product forward.

Early stages

Like Polytherics, much of the work on new interferons are at early stages. The table below shows interferon alphas are most commonly being investigated, with a lot of companies attempting new pegylation technologies.

In terms of clinical development, Bristol-Myers is clearly leading the pack, although alongside Biolex others are pushing ahead with novel technologies.

For example Digna Biotech started a phase I/II study earlier this year with its interferon alfa-5 product. An

interferon subtype that is produced in the liver of healthy patients, the product is manufactured through recombinant DNA technology, using *E. coli*.

Despite all this work, it seems unlikely that a greatly improved interferon will reach the market anytime soon.

Ultimately, the goal is removing the need for interferons completely. Although combinations of various new anti-virals are looking promising, this remains on the distant horizon.

“Most of us think the future, if we’re fortunate, lies in combinations of oral agents that will bypass interferons,” says the Royal Free’s Dr Dusheiko. “But that is still hypothetical.”

In the meantime, if the new wave of anti-virals can be followed by much more tolerable interferons, this will still represent great progress for hep C patients.

Selected interferons in development for hepatitis C

	Product	Pharmacological Class	Company
Phase II	PEG-IFN-lambda	Interferon lambda	Bristol-Myers Squibb
	IFN-alpha-XL	Interferon alpha	Flamel Technologies
	HDV-IFN	Interferon	Hepasome Pharmaceuticals
	Oral HDV-IFN	Interferon	Hepasome Pharmaceuticals
	NAHE001	Interferon alpha	Digna Biotech
	Locteron	Interferon alpha	Biolex Therapeutics/OctoPlus
Phase I	TRK-560	Interferon beta	Toray Industries
	P1101	Interferon alpha	PharmaEssentia
Pre-clinical	HiPEG IFN a-2a	Interferon alpha	PolyTherics
	Interferon-a TheraPEG	Interferon alpha	PolyTherics
	GO 7.1	Interferon alpha	Debiopharm
	HM10660A	Interferon alpha	Hanmi Pharmaceutical
	InferoXen	Interferon alpha	Lipoxen
	Glycoferon	Interferon alpha	Alios BioPharma
	PEG Interferon alpha	Interferon alpha	Ascendis Pharma
	BBT-012	Interferon alpha	Bolder BioTechnology