Evaluate Vantage

May 26, 2011

Therapeutic focus - Gout pipeline looks thin but holds promise

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Positive data presented on Ardea Biosciences' lesinurad (RDEA594) and Novartis' canakinumab in treating gout patients who do not respond to first-line treatments are encouraging developments in treating a disease that has seen few drugs introduced since allopurinol was launched nearly 50 years ago.

This is important because allopurinol's healing powers appearing to be waning as the profile of a typical gout patient has evolved since the 1960s – recent trials suggest just 40% of patients now respond to allopurinol. The last couple of years have seen the launch of two new products, febuxostat and pegloticase, but both drugs have failed to live up to expectations - febuxostat due to reimbursement issues and pegloticase on safety concerns. As such, lesinurad and canakinumab could be much-needed new treatment options to emerge from a pipeline that is surprisingly thin for such a widespread condition (see table below).

Evolving disease

Caused by a build up of uric acid crystals in the joints, gout is a chronic inflammatory disease associated with progressive pain and joint destruction, and the development of disfiguring tophi or nodules on the affected joints.

Gout treatment was revolutionised when allopurinol, a xanthine oxidase inhibitor, was identified and it had a remarkable impact on treatment – the vast majority of patients responded very well and the drug has been standard of care since then.

However, in the same period the profile of gout patients have changed – they have greater co-morbidities, have become more obese and diets have shifted to include products that greatly increase uric acid, such as high fructose corn syrups.

When Takeda conducted several large pivotal trials of feboxustat, its novel xanthine oxidase inhibitor, allopurinol was used in control arms. "It was really the first time large scale trials of allopurinol were conducted. And people were shocked to find that in 1,200 patients over three trials, it only worked in 40% of patients," says Barry Quart, chief executive of Ardea Biosciences.

Because patients are monitored closely in trials, the result could not have been down to non-compliance, but due to the declining efficacy of allopurinol. "A lot of people have now woken up to the opportunity, we believe it really is a dramatic unmet need," he says. "Gout was pretty much ignored for the last 40 years but in the last five years there's been a real revolution in research and development".

Disappointing

Takeda argues that febuxostat, launched in 2009, is a more potent xanthine oxidase inhibitor than allopurinol, with equivalent efficacy achieved at similar doses. Although the drug sold $106m last year, the company has struggled to get payers to reimburse the drug in favour of cheap allopurinol. The UK's NICE, for example, will only reimburse it if a patient is unable to take allopurinol.

Savient's Krystexxa has also been a disappointment with safety concerns limiting uptake and use of the drug since it was launched at the end of last year. It has been the subject of regular analyst downgrades as specialists estimate just 1-2% of patients, only those with severe and refractory forms of the disease, are candidates for the drug (*Tough quarter for new product launches by small pharma groups, May 11, 2011*).

Looking ahead

Thus, specialists in the field are looking to the pipeline in the hopes of better things to come, and the annual congress of the European League Against Rheumatism has been an opportunity for Novartis and Ardea to disclose new research findings for their pipeline drugs.

In the case of Novartis, the antibody canakinumab, dubbed Ilaris or ACZ885, significantly reduced pain and the

risk of flare ups compared to triamcinolone acetonide in those patients with severe gouty arthritis who do not respond to standard NSAIDs or colchine, or for whom those treatments are inappropriate.

Meanwhile, Phase IIb data from Ardea's RDEA594 demonstrated that it provided superior uric acid clearance than placebo in patients who do not respond to allopurinol alone (*EULAR - Ardea's gout drug striving for sizeable second line slice, May 26, 2011*).

Mr Quart believes lesinurad represents the next breakthrough because 90% of gout patients have defects in their ability to excrete uric acid – essentially their kidneys do not work efficiently enough to get rid of the uric acid their body is producing. Only 10% of patients suffer from the disease because of overproduction of uric acid, he says.

So the xanthine oxidase inhibitors, which work by reducing the body's production or uric acid, are not solving the problem for a lot of patients, he argues. Adding lesinurad, however, vastly improves outcomes for patients.

Earlier trials have shown that lesinurad also works as a monotherapy, but with allopurinol available as a cheap generic, it is unlikely to unseat the drug as a first line choice.

"But if we get 60% of the patients who take allopurinol and don't respond, that's fine with us. Plus the 5 to 10% of patients who cannot tolerate allopurinol – that's still a pretty big market," he says.

Of the pipeline products for gout, analysts have put the most optimistic forecasts on these two products, with canakimumab estimated to push the $400m mark in this indication alone.

Advances

Regeneron is due to seek US approval for Arcalyst any time now, to reduce gout flares. Positive data from two phase III trials have been reported, showing the drug significantly reduced gout flares in patients initiating allopurinol therapy – a side effect often seen in patients first starting on the drug. The weekly subcutaneous drug inhibits interleukin-1, an immune system regulator that drives inflammatory responses.

The one remaining pipeline candidate with any analyst forecasts is BioCryst Pharmaceuticals' BCX-4208. It is expected to report Phase IIb data in the fourth quarter, Again, however, it relies on a backbone of allopurinol, being used in patients refractory to the first-line drug, tested in combination with allopurinol against placebo plus allopurinol.

A new candidate has emerged in Metabolex's arhalofenate (MBX-102), which recently entered phase II in the management of hyperuricemia in patients with gout. The phase II trial will compare uric acid clearance in patients taking arhalofenate to those taking placebo over four weeks. The California company also plans a trial using an allopurinol backbone in refractory patients and a combination study with febuxostat.

Although it is decades-old, allopurinol remains a first line option, even with changes in diet and patient population. Should evidence continue to emerge that patients are increasingly not responding, the economic argument for its widespread use will weaken. So although the pipeline remains thin, there is real potential for a new agent to take allopurinol's place – an opportunity that could prompt that pipeline to fill in the coming years.

Gout Market - selected marketed and clinical stage pipeline products					WW annu			
Status	**Product**	**Generic Name**	**Company**	**Pharmacological Class**	**2010**	**2011**	**2012**	**2**
Marketed	Krystexxa	pegloticase	Savient Pharmaceuticals	Urate oxidase	-	28	96	
	Uloric/Adenuric	febuxostat	Takeda + Teijin + Menarini + Ipsen	Xanthine oxidase inhibitor	106	158	200	
	Urinorm	benzbromarone	Torii Pharmaceutical	Uricosuric agent	40	44	43	
	Allopurinol	allopurinol	Multiple branded and generic companies	Xanthine oxidase inhibitor	-	-	-	
	Colcrys	colchicine	URL Pharma	Anti-gout preparation	-	-	-	
Phase III	Arcalyst	rilonacept	Regeneron Pharmaceuticals	IL-1 antagonist	-	-	8	
	Ilaris	canakinumab	Novartis	Anti-IL-1-beta MAb	-	40	100	
	FYX-051	topiroxostat	Fuji Yakuhin + Suzuken	Xanthine oxidase inhibitor	-	-	-	
Phase II	RDEA594	lesinurad	Ardea Biosciences	URAT1 inhibitor	-	-	-	
	BCX-4208 (R3421)	-	BioCryst Pharmaceuticals	Purine nucleoside phosphorylase (PNP) inhibitor	-	-	-	
	NU1618	tranilast	Nuon Therapeutics + Kissei Pharmaceutical	Xanthine oxidase inhibitor	-	-	-	
	MBX-102/JNJ 39659100	arhalofenate	Metabolex + Johnson & Johnson	Selective PPAR gamma modulator (SPPARM)	-	-	-	
Phase I	Pegadricase	pegadricase	Polaris Group + 3SBio	Urate oxidase	-	-	-	