Evaluate Vantage

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Therapeutic focus - Pfizer data highlights potential of JAKs in arthritis

Just like the oral revolution heading towards the multiple sclerosis market, data from Pfizer yesterday on tasocitinib suggests a similar transformation is possible in rheumatoid arthritis.

Encouraging pivotal data revealed at the ACR rheumatology conference confirms the pill, a JAK-3 inhibitor, is looking as effective and safe as the widely used injectable therapies available such as Humira, Enbrel and Remicade. These three products are expected to generate sales of $13bn in RA this year (see table below); although tasocitinib still has much to prove the potential is clear. As the analysis below shows the Pfizer product is by far the most advanced drug of its class, although several other JAK inhibitors are coming through, most notably a mid-stage candidate from Eli Lilly which also reported promising data at ACR.

Important signalling cascade

Janus kinase inhibitors, or Jaks, are being tested in a range of indications; while the Jak-2s are mostly being trialled in blood disorders like myelofibrosis the Jak-3s are being tested in autoimmune diseases like RA (*Therapeutic focus - Sanofi snaps up rare upartnered JAK-2 inhibitor, July 5, 2010*).

These intracellular protein kinases play a critical role in a pathway by which extracellular signals, such as cytokines and growth factors, stimulate a cellular response. Atypical JAK signalling is implicated in conditions such as myeloproliferative disorders, haematological cancers, inflammation and autoimmunity. For example Jak-dependent cytokines have been implicated in a number of inflammatory and autoimmune diseases like RA, suggesting that Jak inhibitors might be effective in alleviating the disease.

Data emerging from Pfizer and others appears to be confirming this hypothesis. Analysts at UBS describe the JAK class as “real and exciting”.

“The efficacy data is proving to be consistently strong such that the focus of the experts has practically already moved to side effects,” they wrote in a research note today. As the table below shows, consensus forecasts already have tasocitinib as the eighth biggest branded RA treatment by 2016, highlighting the huge expectations around this product, and the class.

Comparable efficacy with few safety issues

The data Pfizer reported at ACR was from a phase III trial called Oral Solo, which was conducted in a challenging population: patients who had failed on at least one disease modifying anti-rheumatic drug (Dmard). The study tested two doses of tasocitinib against placebo on three primary measures over six months; two were met and one was missed, but a trend towards efficacy was seen.

On safety, no new issues were seen and importantly there were no cases of opportunistic infections, a big problem with the anti-TNF agents like Humira and Enbrel, which suppress the immune system.

As the table below shows these anti-TNFs dominate the branded segment of the market – methotrexate is widely used as the first-line therapy for RA but is now available generically, and is not included in the analysis.

Because of their side effects the injected anti-TNFs are reserved for moderate to severe patients, many of whom will already be taking methotrexate. An oral pill instead of injections would present an attractive option for patients.

However the Jak inhibitors coming through are going to be held up against these dominant incumbents and they must at the very least be as safe – the potential complications of the anti-TNFs means that some doctors and patients might be willing to sacrifice some efficacy if a much better safety profile emerges.

Branded Rheumatoid Arthritis market				Annual Indication Sales WW ($bn)			
Rank	**Product**	**Company**	**Pharmacological Class**	**2010**	**2013**	**2016**	**Status**
1	Humira	Abbott Laboratories/Eisai	Anti-TNFa MAb	5.02	6.17	6.41	Marketed
2	Enbrel	Amgen/Pfizer/Takeda	TNFa inhibitor	4.43	4.98	5.00	Marketed
3	Remicade	Johnson & Johnson/Merck & Co/Mitsubishi Tanabe Pharma	Anti-TNFa MAb	3.52	3.65	3.51	Marketed
4	Simponi	Johnson & Johnson/Merck & Co	Anti-TNFa MAb	0.30	1.46	2.21	Marketed
5	Actemra	Roche/Chugai	Anti-IL-6 MAb	0.38	1.34	2.17	Marketed
6	Orencia	Bristol-Myers Squibb	B7 integrin antagonist	0.75	1.27	1.65	Marketed
7	Rituxan	Roche	Anti-CD20 MAb	1.23	1.57	1.37	Marketed
8	Tasocitinib	Pfizer	Janus kinase-3 (JAK-3) inhibitor	-	0.25	1.02	Phase III
9	Cimzia	UCB/Otsuka	Anti-TNFa MAb	0.16	0.58	0.89	Marketed
10	R788	AstraZeneca	Syk kinase inhibitor	-	-	0.79	Phase III
			Total Branded Market	**16.29**	**21.93**	**26.07**	

This is only the first set of phase III data Pfizer has released on tasocitinib and much more is expected in the first half of next year. The company is running six pivotal trials in various patient populations, and could file for approval towards the end of 2011, if all goes well.

Studies are testing the drug in patients who do not respond to anti-TNFs and in combination with other therapies, while a large 700-patient study is comparing the drug against Humira.

Analysts are pencilling in a launch in 2012 and blockbuster status by 2016, but this number is highly susceptible to change over the coming months with further pivotal data. Analysts at Bernstein point out that the drug still has to generate evidence it works over the long term and prevents bone destruction, while safety has to be at least comparable to the injected Dmards.

The only other Jak that analysts are ascribing sales forecasts in RA is LY3009104, an Incyte candidate partnered with Eli Lilly. Phase IIa, 24-week data presented at ACR showed patient's symptoms were alleviated after 12 weeks; the results prompted UBS analysts to describe efficacy so far as comparable to tasocitinib with possibly a better safety profile.

The other candidate in mid-stage development is Vertex Pharmaceuticals' Jak-3 inhibitor VX-509, which is currently undergoing a 12-week phase II trial in 200 moderate-to-severe rheumatoid arthritis patients; results are due next year.

First in class is not necessarily best in class, but so far Pfizer's candidate is looking promising and first to market would definitely be a huge advantage. And there are other mechanisms of actions that might also deliver an advanced oral pill, for example R788, or fostamatinib disodium, is a spleen tyrosine kinase (Syk) inhibitor in phase III trials. AstraZeneca licensed the drug from Rigel Therapeutics for $100m upfront earlier this year (*Therapeutic focus - Rheumatoid arthritis pipeline full but deals dropping off, July 10, 2009*).

A lot of safety and efficacy data is still required but an oral revolution for RA could be on the way.

Jak inhibitors in development for RA				Annual Sales WW
	Product	**Company**	**Pharmacological Class**	**2016**
Phase III	Tasocitinib	Pfizer	Janus kinase-3 (JAK-3) inhibitor	$1.02bn
Phase II	LY3009104	Eli Lilly/Incyte	Janus kinase-1/2 (JAK-1/2) inhibitor	$60m
	VX-509	Vertex Pharmaceuticals	Janus kinase-3 (JAK-3) inhibitor	-
Phase I	GLPG0634	Galapagos	Janus kinase-1/2 (JAK-1/2) inhibitor	-
	R348	Rigel Pharmaceuticals	Janus kinase-3 (JAK-3) inhibitor	-
	PRT062607	Portola Pharmaceuticals	Syk kinase & janus kinase (JAK) inhibitor	-

All data sourced to EvaluatePharma.