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Therapeutic focus – Interleukin modulators crowd pipeline for severe asthma

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By mid-2014 the industry should have a good idea of whether attacks of a severe form of asthma can be prevented by suppressing immune response. Phase III trials of Teva's Cinquil are expected to wrap up sometime this year, while GlaxoSmithKline's mepolizumab should report mid- and late-stage data in the first half of next year. This will give researchers a sense of how well eosinophilic asthma can be controlled by modulating the action of interleukins.

Last week, Sanofi and Regeneron Pharmaceuticals reported positive phase II data from their antibody dupilumab, which when combined with an anti-inflammatory and bronchodilators significantly reduced the frequency of asthma attacks compared with placebo. The space is getting crowded, however – a scan of the pipeline shows at least 10 antibodies seeking to improve exacerbations, and small-molecule kinase inhibitors are also trying to elbow their way in (see table).

Wrong reaction

Somewhere around half of all asthma is believed to be of allergic origin related to inflammation caused by eosinophils – white blood cells that are responsible for fighting multicellular parasites and other infections, but which also play a role in allergic response. Dysfunctional allergic response leads to chronic inflammation of airways, and puts patients at higher risk of asthma attacks.

Patients can be identified by elevated eosinophil counts in their sputum, and indeed such elevations can begin developing weeks before an attack. Thus, patients with poorly controlled asthma could benefit from lowered eosinophil counts, offering the potential of a therapy that could treat the underlying disease processes rather than symptomatic control offered by corticosteroids and beta 2 adrenoreceptor agonists. It is estimated that some 38 million people in the USA will suffer from an eosinophilic asthma event in their lifetime.

The leading candidates in the space are antibodies that aim to bind to interleukins, which signal the maturation, recruitment and survival of eosinophils. However, another approach to blocking the signalling cascade is to bind to interleukin receptors, which is what the Sanofi and Regeneron antibody does, along with Aerovance's recombinant protein Aerovant, now in phase II, which unlike the antibodies has been tested as an inhaled dry powder formulation.

Clinical-stage candidates for eosinophilic asthma						
	Product	**Generic name**	**Pharmacology class**	**Company**	**Originator**	**Trial ID**
Phase III	Bosatria	mepolizumab	Anti-interleukin-5 (IL-5) MAb	GlaxoSmithKline	SmithKline Beecham	NCT01691 NCT01691
	Cinquil	reslizumab	Anti-IL-5 MAb	Teva Pharmaceutical Industries	Schering-Plough	NCT01270 NCT01285 NCT01508 NCT01287 NCT01290
Phase II	AIN457	secukinumab	Anti-IL-17 MAb	Novartis	Novartis	NCT01478
	RG3637	lebrikizumab	Anti-IL-13 MAb	Roche	Tanox	First patien in PhIII Q3 2013
	AMG 827	brodalumab	Anti-IL-17 MAb	AstraZeneca/Amgen	Amgen	NCT01199
	REGN668/ SAR231893	dupilumab	Anti-interleukin-4 receptor (IL-4R) MAb	Sanofi/Regeneron Pharmaceuticals	Regeneron Pharmaceuticals	NCT01312
	Benralizumab	benralizumab	Anti-IL-5 MAb	AstraZeneca/Kyowa Hakko Kirin	Kyowa Hakko Kogyo	NCT01238 NCT01412
	ABT-308	-	Anti-IL-13 MAb	AbbVie	Abbott Laboratories	NCT00986
	QAX576	-	Anti-IL-13 MAb	Novartis	Novartis	NCT01479
	CAT-354	tralokinumab	Anti-IL-13 MAb	AstraZeneca	Cambridge Antibody Technology	NCT01402
	Aerovant IV	pitrakinra	IL-4 & IL-13 antagonist	Aerovance	Bayer	NCT00801
	Aerovant	pitrakinra	IL-4 & IL-13 antagonist	Aerovance	Bayer	-
	R343	-	Spleen tyrosine kinase (Syk) inhibitor	Rigel Pharmaceuticals	Rigel Pharmaceuticals	NCT01591
Phase I	GSK2434735	-	Anti-IL-13 MAb	GlaxoSmithKline	GlaxoSmithKline	NCT01563

Results soon

First up will probably be Teva's Cinquil, a product picked up with Teva's acquisition of Cephalon in 2011 (*Teva strives to meet growth targets with Cephalon buy, May 3, 2011*). The monoclonal antibody has struggled to get any respect from analysts, who have yet to include it in their forecasts for the Israel-based group (*Event – Teva looks to brand new success with Cinquil, December 3, 2012*).

In phase II, the agent, infused intravenously, significantly improved lung function and reduced sputum eosinophils over 12 weeks compared with placebo, but just missed significance on improvements in asthma control questionnaire scores.

GlaxoSmithKline's Bosatria, which like Cinquil binds to IL-5, will be the next to read out phase III data, probably next year. Its phase III programme tests a subcutaneous and intravenous formulation, and will measure not only rates of exacerbations and lung function but also how well it reduces use of steroids and prevents exacerbations triggered by rhinovirus infections.

Expectations are growing for this candidate, with $229m in sales forecast for 2018, according to *EvaluatePharma*'s consensus. However, should it make it to market as predicted in 2016, it would mark a significant delay from original plans – the UK group had filed for European approval in hypereosinophilic syndrome and withdrew it after feedback from regulators.

A third candidate nearing late-stage trials is Roche's lebrikizumab, or RG3637, an IL-13 antibody. This has two active phase II trials, but the Swiss company announced in October that it still needed to optimise manufacturing, and thus would be delaying pivotal work. Regulatory filing is not expected until after 2016.

Shotgun approach

Phase II has a mix of targets: IL-4, IL-5, IL-13 and IL-17. In addition to the Sanofi/Regeneron and Aerovance receptor targeting, Novartis has two agents in secukinumab and QAX576, targeting IL-17 and IL-13 respectively; AstraZeneca has three in AMG 827, benralizumab and CAT-354, which have emerged from partnerships with Amgen, Kyowa Hakko Kirin and Cambridge Antibody Technologies, and hitting IL-17, IL-5 and IL-13 respectively; and AbbVie's ABT-354, focusing on IL-13. AMG 827 is also known as brodalumab, and is nearing a major phase III readout in psoriasis.

It is only in phase II that a different pathway is being targeted. Rigel Pharmaceuticals' R343, a spleen tyrosine kinase (Syk) inhibitor, binds to mast cells and disrupts signalling from immunoglobulin E, a cascade that also plays a role in eosinophilic asthma.

Should the interleukin antibodies turn out less than promising in late-stage trials, it seems Rigel's kinase inhibition approach could be the next opportunity to address the disease. Astra has gotten in on the ground floor here and locked up one of Rigel's kinase inhibitors, a janus kinase that modulates the IL-13 pathway (*Therapeutic focus - Astra and Rigel throw a JAK into the cytokine-targeting asthma box, June 21, 2012*).

Even if the antibody approaches turn out effective, it may be that the tyrosine kinase products are preferable; as inhalation drugs, they would be attractive to a greater share of patients. As the interleukin-targeting antibodies begin to reach their pivotal readouts over the next couple of years, it will help clarify what sort of role the small molecule candidates might play.

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