Evaluate Vantage

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Therapeutic focus – Amyloidosis options emerging from Pfizer, Alnylam

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A phase I product targeting a rare inherited disorder is increasingly moving into the spotlight for Alnylam. Following news yesterday of the failure of the US company's most advanced clinical candidate, lung infection treatment ALN-RSV01, approaching early-stage data on the amyloidosis agent takes on greater importance.

Being investigated in hereditary amyloidosis or ATTR, ALN-TTR02, has shown encouraging signs of efficacy in an illness characterised by the accumulation of protein deposits in various tissues of the body, a progressive and fatal condition that can only be treated currently with a liver transplant. A Pfizer candidate, Vyndaqel, which targets the neurological impairment suffered by some patients, received a mixed reception from an FDA panel earlier this month, while GlaxoSmithKline has another closely watched phase I candidate in development. With a handful of companies working on treatments for the three major types of systemic amyloidosis – all of which hit that orphan drug sweet spot – signs of clinical success stories are awaited (see table).

Amyloidosis

The accumulation of protein deposits – amyloids – are associated with a number of diseases including Alzheimer's, Huntington's and atherosclerosis. Caused by different proteins that gather and tangle in different parts of the body, amyloidosis lies at the root of several diseases that manifest throughout the body.

The three major types of systemic amyloidosis are primary (AL), secondary (AA) and hereditary (ATTR). The A stands for amyloid while the second letter represents the protein type that accumulates.

Primary amyloidosis occurs when plasma cells in the bone marrow overproduce immunoglobulin light chain (L), which can form toxic aggregates leading to amyloid deposition. This accumulates in several organs, including the heart, liver, lungs and kidneys, and can arise from diseases such as multiple myeloma.

Secondary amyloidosis most commonly progresses from chronic inflammatory diseases such as RA, causing amyloid A to accumulate in major organs, particularly the kidneys, causing organ failure and eventually death.

Meanwhile hereditary amyloidosis, or ATTR, is an autosomal dominant genetic disease, caused by mutations in the gene encoding the transthyretin (TTR) protein. The protein is misfolded, leading to its accumulation in tissues such as the heart, gastrointestinal tract and peripheral nerves. TTR is primarily produced in the liver, hence the use of liver transplant as a final resort treatment for the progressive and fatal condition.

Where TTR accumulates in the heart muscle, leading to heart failure, the disease is called familial amyloid cardiomapthy or FAC; this is thought to affect more than 40,000 patients worldwide. Familial amyloid polyneuropathy, or FAP, which affects more than 10,000 people worldwide, occurs when TTR accumulates in the peripheral nerve tissue, causing wasting and a loss of nerve function.

Patients with FAP – the target of Pfizer's agent Vyndaqel or tafamidis – have a mean life expectancy of 5-15 years from onset of symptoms, which can appear as early as the 30s.

Targeting TTR

Pfizer's Vyndaqel drug works by stabilising TTR, preventing the formation of misfolded proteins and amyloid deposits. At the end of last year it was approved in Europe; however mixed results from the phase III programme mean its chance of reaching the US market are less clear.

Although the trials demonstrated trends to neurological improvements, the primary measures of the trials, the pivotal programme failed to prove this statistically. European regulators granted approval on the basis of assays which demonstrated transthyretin stabilization in 98% of patients after 18 months.

This month an FDA advisory panel voted 13-4 that data on the drug did not show substantial evidence of efficacy on a clinical endpoint – the neurological measures – although they did vote 13-4 that the data provide substantial evidence of efficacy for a surrogate endpoint that is reasonably likely to predict a clinical benefit – the assay reading.

The FDA’s final verdict is awaited in June, and given the unmet need in the patient population, approval cannot be completely ruled out.

Different approach

Alnylam and Glaxo, meanwhile, are targeting TTR at the RNA level.

Alnylam is using RNA interference, employing siRNA molecules to target the TTR gene, silencing the TTR protein.

After achieving proof of concept with an earlier molecule, ALN-TTR01, the company is now working on a second generation drug, ALN-TTR02.

ALN-TTR01 at the highest dose produced an average 41% reduction in TTR levels; it is hoped ’02 matches this potency at a much lower dose. Data from a phase I study is expected in the third quarter and the company has already mapped out plans to start a phase II in the second half of this year.

The Alnylam product, which is delivered intravenously, is at a similar stage to a subcutaneous product being developed by Glaxo and partner Isis. In results published early this year, subjects given two doses showed a mean reduction in TTR level of 44% and 81%. The companies are planning further clinical studies evaluating patients with FAP this year.

Comparing the Isis and Alnylam candidates, analysts at Leerink Swann note that the Alnylam program ideally needs to differentiate itself on potency and frequency of administration – it could potentially be given once a month versus once a week. However, the analysts believe that both drugs may be approvable and that the market should be big enough for both to be successful.

Alnylam meanwhile has a preclinical program, ALN-TTRsc, using a delivery approach called GalNAc which is administered subcutaneously. In preclinical studies, once-a-week dosing produced sustained silencing of TTR over a multi-week period. The company is planning to file the IND in the second half of 2012.

Selected amyloidosis pipeline					
	Product	**Company**	**Indication**	**Pharmacological Class**	**Trial ID**
Approved	Vyndaqel	Pfizer	Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP)	Transthyretin stabilizer	NCT00409175 NCT00791492
Phase III	Kiacta	Celtic Therapeutics/BELLUS Health	AA Amyloidosis	Glycosaminoglycan mimetic	NCT00035334 NCT01215747
Phase II	Treanda	Teva Pharmaceutical Industries	Relapsed AL Amyloidosis	Alkylating agent	NCT01222260
	Revlimid	Celgene	AL Amyloidosis	Immunomodulator	NCT00607581 NCT00091260
Phase I	ALN-TTR01	Alnylam Pharmaceuticals	Transthyretin-mediated amyloidosis (ATTR)	Transthyretin RNAi therapeutic	NCT01148953
	MLN9708	Takeda	Relapsed or Refractory AL Amyloidosis	Proteosome inhibitor	NCT01318902
	ISIS-TTRRx	GlaxoSmithKline/Isis Pharmaceuticals	Transthyretin-mediated amyloidosis (ATTR)	miRNA antisense	-
	ALN-TTR02	Alnylam Pharmaceuticals	Transthyretin-mediated amyloidosis (ATTR)	Transthyretin RNAi therapeutic	NCT01559077
	GSK2315698	GlaxoSmithKline	Systemic Amyloidosis	Metabolic disease agent	NCT01406314 NCT01323985
	Systebryl	ProteoTech	AA Amyloidosis	AA amyloid fibril inhibitor	-
Pre-clinical	NEOD001	Elan	AL amyloidosis	Metabolic disease agent	-
	ALN-TTRsc Program	Alnylam Pharmaceuticals	Transthyretin-mediated amyloidosis (ATTR)	Transthyretin RNAi therapeutic	-

Other amyloids

Outside of the inherited form of amyloidosis work is also progressing, although the pipeline is thinner.

Working in AA amyloidosis is Bellus with Kiacta, which is being tested as a preventive treatment, designed to stem renal function decline.

Although it is the most common form of systemic amyloidosis it is still incredibly rare. Bellus says that it is estimated that 50,000 people living with the disease in the US, Europe and Japan although other estimates put the figure at much lower - 3,000 in the US for example.

Diagnosed patients quickly progress to dialysis and typically die within five years; with no treatment available an agent to delay or even prevent dialysis would therefore be in demand.

The development path for Kiacta, which won orphan drug designation in the US and Europe more than 10 years ago, can certainly be described as tortuous. In 2008 Johnson & Johnson handed the rights back to Bellus – then called Neurochem - after a couple of years trying and failing to convince regulators to grant approval. A phase

II/III study suggested that the drug, generically called eprodisate, was effective at slowing down progressive renal failure, but the trial failed to meet the primary endpoint of reducing the number of patients whose kidney function got significantly worse or who died over two years.

The CHMP requested further data and the company withdrew its US application before a likely FDA rejection.

A glycosaminoglycan mimetic which works by inhibiting the deposition of amyloid, Kiacta is undergoing a confirmatory phase III study, funded by Celtic Therapeutics in collaboration with Bellus. As of May 15, 90 patients of the 230 sought had been enrolled in the trial, Bellus said. The event-driven trial will conclude when 120 patients have reached worsening events linked to deterioration of kidney function; results are not expected until 2014.

Working on a much earlier compound is ProteoTech with Systebryl. According to the company, pre-clinical animal studies showed that the oral product caused a marked prevention of AA amyloid fibril formation and a marked reduction and clearance of pre-existing AA amyloid fibril deposits. Phase 1a human clinical trials have been completed and ProteoTech says it hopes to advance the drug through Phase 2a proof-of-concept trials this year.

Primary AA

Work in primary amyloidosis, driven by the overproduction of light chain immunoglobulin, is largely ongoing in agents currently approved to treat cancers of the bone marrow and blood. In this form, proteins accumulate in organs such as the heart and kidneys, causing rapidly progressive heart failure and worsening renal function.

AL amyloidosis can arise from diseases such as multiple myeloma. Current therapy options aim to reduce the supply of light chain by suppressing the underlying proliferation of plasma cells, such as the use of cytotoxic regimens. The median survival of untreated patients is 13 months from diagnosis; with the use of the alkylating agent melphalan and the steroid prednisone this can be increased to 16-18 months.

Stem cell transplantation can prolong survival substantially. However, it is only suitable for a small number of patients. In the US there are only 1,200-3,000 new cases reported each year, while approximately 500-600 people are diagnosed each year in the UK.

Chemotherapy agent Treanda, approved to treat chronic lymphocytic leukaemia and non-hodgkin lymphoma, was slated for study in these patients, although the trial, listed on clinicaltrials.gov, is not yet open for recruitment.

Meanwhile Revlimid is in a phase II trial in previously treated patients with AL amyloidosis. The multiple myeloma treatment is being tested in combination with cyclophosphamide and dexamethasone. According to clinicaltrials.gov the trial completed in January this year, although no results have yet been published.