Evaluate Vantage

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Therapeutic focus - AstraZeneca makes rare advance with sepsis treatment

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News yesterday that AstraZeneca is pressing ahead with an experimental sepsis treatment, a polyclonal antibody fragment called CytoFab which will enter a large phase IIb trial early next year, is encouraging for a field that is in desperate need of effective treatments.

There is only one product approved to specifically address the life threatening condition, Eli Lilly's Xigris, and very little in the industry's R&D pipeline (see table below). Around 3 million people worldwide are thought to be affected by sepsis each year, and the disease has a high mortality rate of around 30%, resulting in about 215,000 deaths in the US alone. The fact that Astra has taken so long to move forward with CytoFab, which it licensed in late 2005 as a phase III ready product, serves to illustrate how challenging this indication is.

Sepsis or septic shock often develops as a complication after common bacterial infections, when an exaggerated immune response can lead to organ failure and death. The complex illness is very hard to treat and numerous approaches have failed over the last few decades.

Disappointing but notable

There were high hopes that Xigris, a recombinant form of human activated protein C, would offer an effective treatment for patients already suffering organ failure. Although trials established that the drug lowered the risk of death, by 6%, in absolute terms this is not a huge benefit when weighed against the risks, notably of dangerous bleeding events.

This, combined with its high cost, has meant that Xigris has been a fairly big disappointment for Lilly, with uptake far lower than initially expected, as the drug is only used in very severe cases. Lilly started a new trial of Xigris in early 2008 in an attempt to better define the risk-benefit profile of the drug, which should report towards the end of 2010.

Sales forecasts have been gradually coming down for Xigris over last couple of years; consensus for 2012 sales currently sits at $122m, down from $199m two years ago. Sales peaked four years after launch, in 2005 at $215m, and having been sliding since.

Only last February the FDA said it was investigating serious bleeding associated with the drug, suggesting that should another product make it to market, it will not take much to lure business away from Xigris. Still, although Xigris has disappointed, the fact remains that this is still the first new treatment for decades to reach the market for sepsis, a notable achievement.

Septic shock products							
				Annual Sales WW - Sales			
Market Status	**Product**	**Company**	**Pharmacological Class**	**2008**	**2010**	**2012**	**2014**
Marketed	Xigris	Eli Lilly	Protein C concentrate	161	128	122	117
Phase III	E5564	Eisai	TLR4 antagonist	-	36	216	306
Phase II	CytoFab	AstraZeneca	Anti-TNFa polyclonal FAb	-	-	-	-
Phase I	Stedivaze	Clinical Data	Pharmacologic stress agent	-	-	16	75
	Talactoferrin	Agennix	Immunostimulant	-	-	-	-
	EZN-2232 (rhMBL)	NatImmune	Mannan-binding lectin (MBL)	-	-	-	-
	EA-230	Exponential Biotherapies	Immunomodulator	-	-	-	-
Pre-clinical	MEDI-541	AstraZeneca/Cornerstone Therapeutics	Anti-HMGB-1	-	-	-	-
	Viradin	NexBio	Anti-viral	-	-	-	-
	FX107	Fibrex Medical	Immunosuppressant	-	-	-	-
	HMGB1 BoxA	Nautilus Biotech	Anti-HMGB-1	-	-	-	-
	AB103	Atox Bio	Superantigen antagonist	-	-	-	-
	Traumakine	Faron Pharmaceuticals	Interferon beta	-	-	-	-

Source: EvaluatePharma

Late-stage chances

There is only one product in late stage development for sepsis, Eisai's immunosuppressant E5564, which entered phase III in 2006. Data could be due anytime soon; the Japanese company has said it plans to file for approval in the US, EU and Japan this year.

The drug is a TLR4 (toll like receptor) antagonist, designed to block the activities of bacterial endotoxins that play a key role in the development of sepsis. However, with only one TLR having made it to the market, a topical anti-infective called Aldara, and many abandoned along the way, this is a high risk approach. Takeda's similar drug, TAK-242, was abandoned in sepsis in February of this year (see table below).

This lack of research leaves Astra's CytoFab as the next most advanced candidate. Originated by Britain's Protherics, which was subsequently bought by BTG, Astra bought rights to the drug in a deal worth up to £195m, including £16m upfront. At that point positive phase IIb data had been generated showing that CytoFab caused a marked reduction in the inflammatory mediator TNF-alpha in the blood and lung tissues of patients with severe sepsis, and patients required less mechanical ventilation. A trend to survival benefit was also seen.

A pivotal trial was due to start in 2007, however, regulators requested further phase II work which Astra appears to have pushed forward with very cautiously. Albeit a long time coming, news that this large phase IIb study in 300 patients will now start is encouraging. The list below of the products abandoned for sepsis reveals that many anti-TNF approaches have failed in late stages, an expensive eventuality that Astra was no doubt keen to avoid.

None of the products in phase I development have sepsis as a primary indication, therefore the chances of success with these are slim, if not very far away.

However, one product that might receive some attention in the not too distant future is Atox Bio's immunomodulator peptide, AB103, which was originally developed as superantigen antagonist for the treatment of toxic shock. In June, the company formed an R&D joint venture to continue the development of the product for sepsis and septic shock. The collaboration includes advanced pre-clinical studies and a phase I clinical trial to be performed at the University of Maryland in the US, supported by a $575,000 grant from the Israel-U.S. Binational Industrial Research and Development Fund (BIRD).

Abandoned products for septic shock				
	Pharmacological Class	**Product**	**Company**	**Indication Comment**
Abandoned Filed	Anti-septic shock MAb	E5	Pfizer	JUN97 Product abandoned (was filed).
Abandoned Phase III	Anti-TNF MAb	Human anti-TNF	Bayer AG	Abandoned in 1997 after disappointing phase III results
		Murine anti-TNF	Bayer AG	Abandoned in 1997 after disappointing phase III results
	Anti-TNFa MAb	Segard	Abbott Laboratories	JUN 2001 In PIII for sepsis. FEB 2000 In PII for the treatment of sepsis & septic shock.
	Platelet activating factor acetylhydrolase	Pafase	ICOS	DEC 2002 IDMC recommend termination of PIII.
	TLR4 antagonist	TAK-242	Takeda	FEB09 Abandoned in PIII - discontinued further development.
	TNF inhibitor	Tenefuse	Roche	1998 Dropped because of lack of efficacy.
Abandoned Phase II	Anti-CD14 MAb	IC14	ICOS	FEB 2004 Abandoned after failure of PII to show efficacy.
	Endotoxin antagonist	E5531	Eisai	DEC 2000 Abandoned in PII trials.
	Factor Xa & IIa inhibitor	BIBT 986	Boehringer Ingelheim	Assumed abandoned in PII - product not mentioned since APR03.
	Nitric oxide synthase inhibitor	546C88	GlaxoSmithKline	1999 abandoned following an internal company review of projects.
	Phospholipid anti-endotoxin emulsion	270773	GlaxoSmithKline	OCT06 PII discontinued following an unfavourable risk/benefit assessment.