First IL-6–blocking drug nears approval for rare blood disorder

Last month, Janssen R&D submitted applications to drug regulators on both sides of the Atlantic in hopes of obtaining licensure for the New Jersey company's antibody drug siltuximab for the treatment of multicentric Castleman's disease (MCD), a rare disorder of the lymphatic system affecting only around 1,000 people worldwide.

"What we know from clinical trials is that patients do well on siltuximab for a long time, up to at least five years," says Jessica Vermeulen, a senior director of oncology at Janssen's biologics division in the Netherlands who led the clinical development of siltuximab in Castleman's disease. "It's a transformational drug for patients with this rare disease."

If approved, siltuximab would be the first drug that directly targets interleukin-6 (IL-6) to make it to market. But there might be more to come: IL-6 is a proinflammatory cytokine that's been implicated in a range of diseases, including cancer and assorted autoimmune conditions. Currently, several drug companies have IL-6–targeting antibodies in various stages of preclinical and clinical development for the whole spectrum of diseases that have been linked to the cytokine (see 'A walk down the IL-6').

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The most pronounced association between IL-6 and disease has been in Castleman's. The illness is characterized by an overproduction of B cells in the lymph nodes that is most often caused by an excessive release of IL-6, a key mediator of B cell growth. Disease that's restricted to only one lymph node—known as unicentric Castleman's disease—can be treated with surgery, but this is a less successful approach for those with MCD, which affects the lymphatic system more broadly. Around half of all cases of MCD are associated with HIV and human herpesvirus 8; these can be treated with drugs that target the underlying infections. However, there are few effective treatment options for people with HIV-negative MCD. Clinicians currently turn to steroids or chemotherapeutics, which can decrease symptoms of inflammation or B-cell growth but which cannot be used long term, or rituximab, an antibody against a B cell protein that can be effective in some cases.

Against this backdrop, siltuximab "is a major advance," says Jim Johnston, executive director of the International Castleman's Disease Organization, based in Santa Fe, New Mexico. "It's not a cure, but it will lessen the symptoms and improve quality of life."

In an open-label phase 1 trial involving 37 people with MCD, 32 experienced at least one clinically beneficial response to siltuximab treatment, and 12 saw their tumors shrink by at least 50% (*Clin. Cancer Res.* **19**, 3659, 2013). Trial investigator Razelle Kurzrock, senior deputy director for clinical science at the University of California–San Diego, recalls one particularly dramatic response. "I had a woman in her 40s with tumors all over her chest and face," Kurzrock says. "She could see the tumors disappearing within two hours of a siltuximab dose, and it's such a benign drug that she could go out on a run right after taking it."

However, it's the results of 79-person placebo-controlled trial that formed the basis of siltuximab's marketing applications. Those data have not yet been made public. According to Vermeulen, they have been submitted for presentation at a scientific conference later this year.

First among an equal?

Siltuximab could become the first marketed drug to target IL-6 directly, but it wouldn't be the first to hit the IL-6 signaling pathway. Actemra (tocilizumab), an antibody co-developed by Switzerland's Roche and Japan's Chugai Pharmaceutical Company, blocks the IL-6 receptor and has been approved for use in people with rheumatoid arthritis in the US, Europe and elsewhere for about four years. It was also approved to treat Castleman's disease in Japan more than eight years ago.

Some researchers are uncertain whether blocking the IL-6 receptor directly will provide unique benefit. "There's no reason to think that targeting the cytokine would be any better than targeting the receptor," says hematologist Frits van Rhee, of the University of Arkansas for Medical Sciences in Little Rock, who has been involved in siltuximab trials. "Having used both antibodies to treat Castleman's, in my view they're equally effective."

The question moving forward is what additional diseases siltuximab and other drugs directed at the IL-6 pathway will be useful for. Janssen is advancing siltuximab in a phase 2 study involving people with an early form of multiple myeloma. However, IL-6–targeted agents have not shown much clinical benefit against cancer, leading most drug companies to now focus on autoimmune disorders such as rheumatoid arthritis.

"For Castleman's, this is a great success story," Kurzrock says, "But for other diseases, where we have not been successful but there are data suggesting that we should have been successful, I think going back and studying the basic science is going to be helpful."

Sarah C P Williams

A walk down the IL-6: Antibody drugs targeting the IL-6 pathway in clinical development.

Target	Drug	Lead company	Partner	Lead indication(s)	Phase
IL-6	Siltuximab	Janssen		Castleman's disease	Application filed
	Sirukumab	Janssen	GlaxoSmithKline	Rheumatoid arthritis	3
	Clazakizumab	Bristol-Myers Squibb	Alder	Psoriatic arthritis, rheumatoid arthritis, Crohn's disease	2
	Olokizumab	R-Pharm Group	UCB	Rheumatoid arthritis	2
IL-6 receptor	Actemra (tocilizumab)	Roche	Chugai	Rheumatoid arthritis	Approved
	Sarilumab	Regeneron	Sanofi	Rheumatoid arthritis	3
	ALX-0061	Ablynx		Rheumatoid arthritis	2

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