Rituxan: re-energizing CFS

By Michael J. Haas, Senior Writer

Even as xenotropic murine leukemia virus-related virus has been taken off the table as a cause of chronic fatigue syndrome, new research from a Norwegian group points to the condition as a B cell disorder and suggests the potential to repurpose Rituxan rituximab and other CD20 antibodies. Indeed, the team reported that Rituxan, an anti-CD20 antibody, improved fatigue symptoms in a Phase II/III trial.¹

The origins of the trial date back to 2003, when physicians at **Haukeland University Hospital** diagnosed a CFS patient with Hodgkin's lymphoma. Over the next several years the patient received four different chemotherapy regimens, one of which included methotrexate, an inhibitor of folate metabolism also known to deplete B cells.²

Only the methotrexate-containing regimen improved the patient's CFS symptoms including fatigue, headaches and muscle pain.³ Because some CFS patients exhibit abnormalities in B cells and other immune cells,⁴ the Haukeland team hypothesized that the patient's improvement resulted from methotrexate's B cell inhibition.

To test their hypothesis, the researchers turned to Rituxan, which specifically targets CD20 on B cells. In an open-label pilot study, two of three patients showed a decrease in CFS symptoms starting six weeks after treatment. The third showed improvement at 26 weeks.

In the study, patients received two doses of Rituxan two weeks apart.

Now, the team has reported results of a Phase II/III study. The double-blind, placebo-controlled trial enrolled 30 CFS patients who received 2 infusions of rituximab or saline. The infusions were given two weeks apart, in doses comparable to the standard dosing of Rituxan to treat rheumatoid arthritis (RA).

The primary endpoint was a significant improvement in patients' self-reported fatigue scores at three months after completion of dosing. The endpoint was a composite of overall fatigue, postexertion exhaustion, the need for rest, and daily functioning.

Secondary endpoints were improvements in fatigue scores assessed at 2-month intervals during 12 months of follow-up. For both primary and secondary endpoints, improvements were deemed significant if they lasted for at least six weeks.

The trial missed the primary endpoint—only 1 of 15 Rituxan patients showed improvements at 3 months. In hindsight, the researchers said the choice of primary endpoint wasn't optimal. In a paper in *Public Library of Science ONE*, the team said it selected the endpoint based on the limited data collected in the prior three-patient trial.

On the secondary endpoints, 10 of 15 Rituxan patients showed improvements 6–10 months after therapy compared with 2 of 15 placebo patients ($p=0.003$). Mean response duration for patients on Rituxan was 25 weeks.

No serious adverse side effects were reported, but two patients in the Rituxan group with pre-existing psoriasis experienced moderate psoriasis worsening.

"We consider the results of this trial to show proof of principle" for the use of B cell–depleting therapies such as Rituxan to treat CFS, team coleader Olav Mella told *SciBX* (see **Table 1, "Repurposing to re-energize"**).

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—Øystein Fluge, Haukeland University Hospital

Table 1. Repurposing to re-energize. Antibodies against CD20 that are marketed or in Phase III testing to treat autoimmune diseases and cancer that could be repurposed to treat chronic fatigue syndrome (CFS).

Company	Product	Type	Status
Biogen Idec Inc. (NASDAQ:BIIB)/ Genentech Inc./Roche (SIX:ROG; OTCQX:RHHBY)	Rituxan rituximab (MabThera)	Chimeric mAb	Marketed to treat multiple sclerosis (MS), rheumatoid arthritis (RA), chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma (NHL); approved for Wegener's granulomatosis and microscopic polyangiitis
Genmab A/S (CSE:GEN)/ GlaxoSmithKline plc (LSE:GSK; NYSE:GSK)	Arzerra ofatumumab	Human mAb	Marketed to treat CLL; Phase III trials to treat RA and NHL
Biogen Idec/Genentech/Roche	Ocrelizumab (RG1594)	Second-generation humanized mAb	Phase III testing to treat primary progressive MS (PPMS) and relapsing-remitting MS (RRMS)
Biogen Idec/ Chugai Pharmaceutical Co. Ltd. (Tokyo:4519)/Genentech/Roche	GA101 (RG7159)	Humanized mAb	Phase III trials to treat CLL and NHL

“Our results point to a biological underpinning of chronic fatigue syndrome,” added coleader Øystein Fluge. “I hope our study will help change the debate around this disease—that it is not psychosomatic or psychiatric—and encourage pharma companies to move into this space.”

Mella is a professor of oncology at the **University of Bergen** and director of the Department of Oncology and Medical Physics at Haukeland. Fluge is a consultant in the same department at Haukeland.

Biogen Idec Inc. and **Roche's Genentech Inc.** unit market Rituxan to treat RA, multiple sclerosis (MS), non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL).

Jan van de Winkel, president and CEO of **Genmab A/S**, agreed that the trial's results suggest Rituxan could treat CFS. “But this is a relatively small study, and the results need to be confirmed in a larger study of perhaps 100 patients to make the clinical benefit of Rituxan clearer” in the disease, he said.

Genmab and **GlaxoSmithKline plc** market Arzerra ofatumumab, a human mAb against CD20, to treat CLL and have the antibody in Phase III testing to treat NHL, DLBCL and RA.

Because GSK has the lead responsibility for developing ofatumumab to treat autoimmune indications, van de Winkel could not say whether the partners would consider repurposing the antibody to treat CFS. GSK declined to comment.

Indications of autoimmunity

Theories about the causes of CFS have ranged from persistent viral infections to metabolic disorders and exposure to environmental toxins. Last month, a consortium of American researchers failed to reproduce a 2009 study linking CFS to a virus called xenotropic murine leukemia virus-related virus (XMRV).⁵⁻⁷ Fluge said the new trial results suggest CFS is primarily an autoimmune disease.

“We think this because we see a delay of several months between treatment and the effect on patients' symptoms,” which is consistent with disease-related autoantibodies remaining in circulation after Rituxan has eliminated the B cells that produced them.

Now, he said, the team's main goal is to identify an autoantibody that could be a marker for CFS. Mella added that the levels of such an antibody could potentially be used to measure responses to Rituxan.

Specifically, the team is looking for an antibody that targets sensory nervous system proteins. “A lot of the disease symptoms appear to be related to nervous system defects,” Mella said. “These patients are often hypersensitive to light and sound and have excessive muscular pain sensations without any obvious source or cause.”

Fluge said those symptoms suggest some nervous system filter is missing in CFS patients, “resulting in massive sensory input.”

To identify the nervous system proteins that might compose such a filter and the antibodies that attack them, the team has collected plasma from healthy controls and CFS patients prior to Rituxan treatment. The group is testing those samples against central and peripheral nervous system proteins from humans and animals.

Van de Winkel said the team's hypothesis about CFS-related autoantibodies was reasonable, but he pointed to an alternate explanation that could not be excluded on the basis on the trial results. Besides producing antibodies, “B cells can also present antigens to T cells and activate them,” he said. “So one could argue that knocking out B cells with Rituxan stops the activation of disease-related T cells.”

Fluge agreed that antigen presentation by B cells to T cells could play a role in CFS. “In our paper we have described this as one possible mechanism for response to B cell depletion, especially in the one patient in our trial who showed a response beginning at two months,” while the effect on antibody production would explain the later responses, he said. “I think both mechanisms could be important” in CFS.

He added that the team is discussing the possibility of conducting a larger, multicenter trial of Rituxan to treat CFS. “But to perform such a study we would have to get some funding either from a partner or the government,” he said.

The team's other follow-on work includes an open-label maintenance trial of Rituxan in 27 of the 30 patients in the Phase II/III trial. “We think most patients will need more than just two infusions of rituximab to have a lasting effect,” Mella said.

The team also is running a Phase II trial of Rituxan in patients with severe CFS.

Bergen Technology Transfer Office A/S holds patents in the U.S. and Singapore covering the use of anti-CD20 antibodies and antibody fragments to treat CFS and has applied for other patents worldwide, said Business Development Manager Torsten Porwol. The IP is available for partnering or licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

Bergen Technology Transfer Office A/S, Bergen, Norway
Biogen Idec Inc. (NASDAQ:BIIB), Weston, Mass.
Genentech Inc., South San Francisco, Calif.
Genmab A/S (CSE:GEN), Copenhagen, Denmark
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Haukeland University Hospital, Bergen, Norway
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
University of Bergen, Bergen, Norway