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Article

## Small Alemtuzumab Trial Finds Molecular Benefits in Some Myositis Patients

SAMSON, KURT

Researchers working with a small group of patients with sporadic inclusion-body myositis (S-IBM) reported that a single, four-day treatment with the monoclonal antibody alemtuzumab (Campath) reduced some of the molecular and cellular inflammatory biomarkers associated with the disease for up to six months, with a corresponding slowing of progressive weakness in some patients.

According to the study's lead author Marinos C. Dalakas, MD, professor of clinical neurosciences and neuromuscular diseases at Imperial College's Hammersmith Hospital, in London, UK, the trial, involving 13 patients, demonstrated proof-of-principle that the immunosuppressive drug might have some beneficial effect and warrants further study in larger trials.

The findings were reported in the June issue of the journal *Brain*.

This was not an efficacy trial, Dr. Dalakas told *Neurology Today* in an e-mail. As reported, alemtuzumab did not significantly improve patients' disability but only induced short-term stability based on the difference between two time periods.

Alemtuzumab is a humanized monoclonal antibody that causes an immediate depletion or severe reduction of peripheral blood lymphocytes. It is used for treating chronic lymphocytic leukemia and T-cell lymphomas and carries significant risk for opportunistic infections. It is also used in some bone marrow and kidney transplants, and has shown some promise in treating multiple sclerosis.

S-IBM, the most common disabling, adult-onset, inflammatory myopathy, is characterized by intense inflammation and, despite T-cell-mediated cytotoxicity, it has been resistant to any kind of immunotherapy.

In the new study, patients received 0.3 mg/kg/day alemtuzumab for four days. Although the study was

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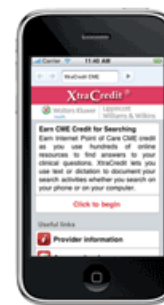
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powered to capture greater than 10 percent increase in strength six months after treatment, and the primary end-point was disease stabilization compared to natural history, patients continued to lose muscle strength, albeit at a slower rate than expected and at a slower rate than did controls.

The major finding was that lymphocytes and T-cell subsets in blood and muscle showed less inflammatory pathology.



Figure. DR. MARINOS

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Depletion of peripheral blood lymphocytes was observed after two weeks and persisted for up to six months, while key effector cells involved in immune response started to increase two months after therapy and peaked by the fourth month.

Total strength from several tests declined in all patients by a mean of 14.9 percent during a 12-month observational period that immediately preceded the trial. Six months after treatment, the total strength score had declined by only 1.9 percent from baseline, according to the report. Among four patients with a 10 percent gain as measured by expected strength loss versus actual loss, six also reported improved performance of daily activities.

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## RISK CONCERNS

Asked to comment on the study, Valerie Askanas, MD, PhD, co-director of the University of Southern California Keck School of Medicine Neuromuscular Center, said in an e-mail that she agreed that the findings are important. But she stressed that more research is needed, especially regarding potential risks and the drug's longer-term ability to slow muscle degeneration.

It is not surprising that powerful immunosuppression can at least transiently help some S-IBM patients, she told *Neurology Today*.

The patients reporting the most benefit had the most significant depletion of T-lymphocytes in their muscle biopsies, suggesting a T-lymphocyte role in the S-IBM pathogenesis. Although in muscle biopsies of alemtuzumab-treated patients there was a significant reduction of transcripts of known stress markers, there was no reduction of transcripts of amyloid-beta precursor protein or ubiquitin, suggesting that the treatment was not affecting what we postulate are key degenerative components of S-IBM muscle fibers, akin to those in the Alzheimer disease brain.

While the authors did not report any adverse reactions, Dr. Askanas noted that all patients were treated as inpatients and were pretreated with several protective drugs before alemtuzumab.

Considering that S-IBM patients are older and often have concurrent illnesses, extra attention should be given to potential side effects of the repeated alemtuzumab treatments and co-administered protective drugs, she said.

The study by Dr. Dalakas, et al., raises the possibility that a safe, more effective method of immunosuppression might be developed to provide a somewhat better long-term mitigation of S-IBM progression; however, she noted that, in her opinion, the degenerative component of the disease

seems to be the essential therapeutic problem to be solved.

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## STUDY DESIGN QUESTIONS

Some researchers were less enthusiastic about the findings, however. Anthony A. Amato, MD, professor of neurology at Harvard School of Medicine and Brigham and Women's Hospital in Boston, questioned the study's design methodology and said he believed the researchers failed to meet their primary endpoint of demonstrating improvement in strength.

While I applaud what Dr. Dalakas has done with his myositis research, I was not impressed with the study, he told *Neurology Today* in a telephone interview.

There were many problems - too few patients, it was open-label, and the design was poor. Really all the paper tells is that in a very small group of patients, treatment was tolerated and safe.

He also expressed concern that some IBM patients and their physicians may take the study at face value, not look as closely as they should at the data, and seek or recommend treatment.



Figure. DR. VALERIE

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[Image Tools](#)

We have already had IBM patients asking for [alemtuzumab] because they have heard of the report, and I know some doctors are already using it.

In response, Dr. Dalakas, told *Neurology Today* that despite the study's size, it did succeed in establishing alemtuzumab's ability to affect beneficial changes in IBM patients on the molecular level.

The study was arguably small and uncontrolled, but taught us a lot about the pathogenesis of IBM, he said in an e-mail. It was not designed to demonstrate efficacy and we do not recommend alemtuzumab as treatment for IBM.

The main finding was a significant reduction of relevant molecules in the repeated muscle biopsies in association with short-term clinical stability. This finding was encouraging and, as we stressed, warrants a controlled study. One should not read more than this into these results.

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## REFERENCE

- Dalakas M, Rakocevic G, Kirk AD, et al. Effect of alemtuzumab (CAMPATH 1-H) in patients with inclusion-body myositis. *Brain* 2009;132:1536-1544.

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