Depleting B cells in atherosclerosis

By Kai-Jye Lou, Staff Writer

Researchers at the **Institut National de la Santé et de la Recherche Médicale** and the **University of Cambridge** have found that B cell depletion can protect mice from atherosclerosis.[1] The results suggest that B cell–reducing therapies being developed by companies for lupus and rheumatoid arthritis could have the added bonus of protecting against cardiovascular disease, which is important because those two patient populations are known to have accelerated development of atherosclerosis.[2]

Previous studies in mice had suggested that B cells themselves play a protective role against atherosclerosis.[3–5] But Ziad Mallat, professor of cardiovascular medicine at the University of Cambridge, saw that those studies did not address B cell depletion and wondered whether depletion would have a negative effect and accelerate the development of atherosclerotic lesions.

Mallat had also noted that "many patients with lupus have already been treated with B cell–depleting therapies like rituximab, and these patients have not shown exacerbation of atherosclerosis."

Rituxan rituximab, a chimeric mAb against CD20, is marketed by **Biogen Idec Inc.** and the **Genentech Inc.** unit of **Roche** to treat various cancers and rheumatoid arthritis (RA).

The answer to the question of whether B cell depletion would increase atherosclerosis was a resounding no. In two immunocompetent mouse models of the disease, depletion of mature B cells with a CD20-targeting mAb led to fewer and less severe lesions than those seen using a control mAb. mAb-mediated B cell depletion also reduced dendritic cell and T cell activation and decreased macrophage and T cell accumulation in atherosclerotic lesions.

Treated mice had less secretion of interferon-γ (IFNG; IFN-γ) from T cells than controls—past studies have suggested that IFN-γ has an overall proatherogenic effect.[6]

The researchers also showed that the atheroprotective effects of mAb-mediated B cell depletion depended on IL-17 (IL-17A). When researchers co-treated mice with a second antibody to neutralize IL-17A, the atheroprotective effects of B cell depletion were lost.

Results were published in *The Journal of Experimental Medicine*.

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> ***—Maureen McMahon, University of California, Los Angeles***

"This work will shed new light on our understanding of the role of the immune system in this common cardiovascular disease," said Mallat, the paper's corresponding author.

"Multiple studies in preclinical models have shown that B cells have an atheroprotective effect, so there have been theoretical concerns that B cell therapies could accelerate the development of atherosclerosis in patients with autoimmune diseases," said Maureen McMahon, an assistant professor of medicine and rheumatology at the David Geffen School of Medicine at the **University of California, Los Angeles**. "What this current work suggests is that the B cell therapies being given to patients with autoimmune diseases may not increase the risk for cardiovascular disease but instead could actually be protective against such diseases."

Results from multiple small clinical studies evaluating rituximab in patients with RA and systemic lupus erythematosus (SLE) have suggested that B cell–reducing therapies could have a positive impact on serum lipid profiles and other biomarkers for cardiovascular disease. However, large-scale studies to demonstrate a decrease in the risk of atherosclerosis and other cardiovascular diseases have not been carried out. No large epidemiological studies have been published.

Genentech spokesperson Amy Berry noted that an association between rituximab use and atherosclerosis has not been demonstrated in the clinic.

Mallat thinks there are a few reasons why previous data showing positive effects of B cells differ from his group's results.

"For example, the animals used in a previous study had their spleens removed, and supplementation with B cells resulted in reduced cholesterol levels. This could have been a confounding factor. Also, the previous studies used immunocompromised mice, and this has been known to produce conflicting study results in the context of autoimmune diseases," he said. The mice used in the current study were immunocompetent.

A new look at old diseases

Despite the observed atheroprotective effects, Mallat thinks expanded use of B cell–targeting therapies to the general atherosclerosis patient population on a long-term basis is unlikely because such drugs may have significant safety risks, such as an increased chance of infections. However, the results reported in *JEM* could change the way researchers evaluate treatments for RA and SLE.

"I think one of the most important implications from the current work is that research on autoimmune diseases is shifting more and more towards studying the relationship between cardiovascular and autoimmune diseases and the impact that B cell therapies will have in this context," said Joaquim Trias, SVP of preclinical development at **Anthera Pharmaceuticals Inc.**

"The study highlighted several pathways known to be involved in atherosclerosis, like interferon-γ and IL-17," said Renee Martin, head

of translational sciences at Anthera. "The results suggest that we may want to rethink how to evaluate the safety profile for therapies being developed to treat autoimmune diseases like rheumatoid arthritis and lupus."

Anthera is developing treatments for both cardiovascular and autoimmune diseases. In June, the company began a Phase III trial of varespladib methyl (A-002) in patients with acute coronary syndrome (ACS). A-002 is a secretory phospholipase A_2 (PLA_2) inhibitor. In July, the company began a Phase IIb trial of A-623 in patients with SLE. A-623, which the company licensed from **Amgen Inc.**, is a fusion polypeptide protein consisting of a BLyS (BAFF) binding domain fused to the Fc region of a human antibody.

"What this study is hinting at is that B cells could have a broader pathogenic role in atherosclerosis than just making antibodies, a function that many consider to protect against the disease," said Dorian Haskard, a professor of cardiovascular medicine at the National Heart & Lung Institute at the **Imperial College London**. "The results suggest that the cellular functions of B cells that regulate T cells and cytokine production could have a larger role in atherosclerosis than the atheroprotective antibody functions."

More patients needed

Researchers contacted by *SciBX* all noted that the results reported in *JEM* will need to be validated in a large, prospective trial.

"Atherosclerosis in the [apolipoprotein E] mouse model used in the current study is very different from atherosclerosis seen in an autoimmune patient, and the lipoprotein profile in mice is also known to be different from that of humans," Trias told *SciBX*.

Anthera's Martin said it would be ideal to carry out a prospective study to assess the risk for cardiovascular events in patients being treated with B cell–targeting therapies. But she added that such a trial would be expensive due to the sheer number of patients that would be required.

"There have been hundreds of lupus patients who have been treated with anti-CD20 therapies like rituximab, but you are going to need a trial with thousands of patients in order to detect a significant change in the risk for cardiovascular events," Martin said.

She said an alternative could be to gather data from large patient registries.

In April 2008, Rituxan missed the primary and all secondary endpoints vs. placebo in a Phase II/III trial in 257 patients with moderate-to-severe SLE. Last March, the companies reported top-line data from the Phase III LUNAR (Lupus Nephritis Assessment with Rituximab) trial showing that Rituxan plus CellCept mycophenolate mofetil missed the primary endpoint of decreasing disease activity in 144 patients with lupus nephritis.

CellCept is a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH). It is marketed by Roche to prevent organ rejection in patients receiving renal, cardiac and hepatic transplants.

Mallat said his group is designing prospective clinical trials to evaluate how B cell depletion therapies affect the risk of cardiovascular disease in 40–50 patients with RA and SLE. "We plan to look at the markers of atherosclerosis in the patients before therapy and after they have been on therapy several months to years."

At a basic science level, Mallat said his group plans to further explore how B cells affect the immune response in atherosclerosis. "We also want to examine the role of the B cell response in more acute complications that can result from atherosclerosis, such as myocardial infarction."

The Institut National de la Santé et de la Recherche Médicale (INSERM) has filed a patent application covering the use of B cell–depleting agents to treat or prevent cardiovascular diseases. The work is available for licensing.

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COMPANIES AND INSTITUTIONS MENTIONED

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Anthera Pharmaceuticals Inc. (NASDAQ:ANTH), Hayward, Calif.
Biogen Idec Inc. (NASDAQ:BIIB), Weston, Mass.
Genentech Inc., South San Francisco, Calif.
Imperial College London, London, U.K.
Institut National de la Santé et de la Recherche Médicale, Paris, France
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
University of California, Los Angeles, Calif.
University of Cambridge, Cambridge, U.K.