Sparing steroids in lupus

By Tim Fulmer, Senior Writer

Researchers at **Dynavax Technologies Corp.** and the **Baylor Institute for Immunology Research** have found that toll-like receptor antagonists could offer a way to lower steroid dosage and thus reduce side effects in lupus patients.¹ Dynavax has a toll-like receptor 7 and toll-like receptor 9 antagonist poised to enter lupus trials within the year.

Lupus is a chronic autoimmune disease characterized by excess production of autoantibodies and proinflammatory cytokines that cause severe damage to multiple tissues, including the skin, joints and kidneys. There are no targeted therapies marketed for lupus. Instead, depending on disease severity, patients receive varying doses of oral or i.v. glucocorticoids in combination with hydroxychloroquine and/or immunosuppressants such as cyclophosphamide and mycophenolate.

Hydroxychloroquine is approved for malaria and for lupus, although its mechanism of action is not entirely clear in the latter.

Compared with other autoimmune indications, lupus often requires high doses of glucocorticoids to reduce the frequency of flares and treat disease, putting patients at risk of a broad range of side effects including hypertension, osteoporosis, hyperglycemia, obesity and retinopathy.

The Dynavax-Baylor team hypothesized that in lupus, unlike in other autoimmune diseases, the anti-inflammatory effects of glucocorticoids are offset by a proinflammatory pathway in immune cells, leading to the need for high-dose steroids. The group reasoned that blocking that unknown proinflammatory pathway could lead to steroid-sparing treatment regimens.

The team first isolated plasmacytoid dendritic cells (pDCs) from lupus patients and tested the response of the cells to glucocorticoids *in vitro*. pDCs are a key contributor to lupus pathogenesis—they bind autoantigen nucleic acids at toll-like receptor 7 (TLR7) and TLR9 and then trigger downstream production of interferon- α (IFN α ; IFN- α) and other proinflammatory cytokines as well as autoantibody-producing B cells (see **Figure 1**, “**Targeting toll-like receptor 7 and 9 in lupus**”).^{2,3}

In the pDCs, glucocorticoids failed to lower production of IFN- α in the presence of two different TLR7- and TLR9-activating ligands. In contrast, glucocorticoids lowered IFN- α production in the presence of a dual TLR7 and TLR9 antagonist.

Those results suggested that signaling through TLR7 and TLR9 made pDCs resistant to glucocorticoids and thus suggested a way to counteract the resistance with dual TLR7 and TLR9 antagonists.

DV1179, a dual TLR7 and TLR9 antagonist from **Dynavax Technologies Corp.** (NASDAQ:DVAX), is in preclinical development to treat lupus; IMO-3100, a dual TLR7 and TLR9 antagonist from **Idera Pharmaceuticals Inc.**, is in Phase I testing to treat autoimmune diseases

MEDI-545, a mAb against IFN- α from **AstraZeneca plc** (LSE:AZN; NYSE:AZN) and **Bristol-Myers Squibb Co.** (NYSE:BMJ), is in Phase II testing for systemic lupus erythematosus (SLE); immunotherapy against IFN- α from **Neovacs S.A.** is in preclinical testing to treat lupus

Figure 1. Targeting toll-like receptor 7 and 9 in lupus. A paper published in *Nature* suggests that inhibiting toll-like receptor 7 (TLR7) and TLR9 in dendritic cells (DCs) could help treat lupus, a disease characterized by high levels of proinflammatory cytokines and autoantibodies that cause damage to multiple tissues.

In lupus patients, immune complexes consisting of double-stranded DNA (dsDNA) and anti-DNA IgG are released from damaged tissues or apoptotic cells and taken up by receptors on the surface of plasmacytoid DCs (pDCs). Once internalized, the immune complexes trigger TLR7 and TLR9 activity in the endosome, leading to activation of pDCs and production of proinflammatory interferon- α (IFN α ; IFN- α) [a].

Secreted IFN- α then stimulates multiple immune cells involved in the autoimmune and antiviral response [b1]. Activated pDCs can also trigger downstream production of B cells that secrete autoantibodies [b2].

In multiple tissues and organs, autoantibodies bind autoantigens [c], forming new immune complexes that cause tissue and organ damage and serve as new sources of autoantigens, completing the vicious cycle [a].

Blocking activation of TLR7 and TLR9 at [a] with a dual TLR7 and TLR9 antagonist could prevent downstream production of proinflammatory IFN- α as well as autoantibody-producing B cells.

In two mouse models of lupus, glucocorticoids plus a dual TLR7 and TLR9 antagonist significantly lowered pDC counts compared with glucocorticoids alone ($p=0.001$). Reductions in pDC levels also correlated with lower expression of IFN- α -regulated genes.

The study, reported in *Nature*, was led by Franck Barrat, director of drug discovery at Dynavax, Robert Coffman, VP and CSO at the company, and Virginia Pascual, principal investigator at the Baylor Institute.

Raising the toll on lupus

The authors wrote that the data “indicate that inhibitors of TLR7 and TLR9 signaling could prove to be effective corticosteroid-sparing drugs.”

David Pisetsky, professor of medicine, immunology and rheumatology at **Duke University**, agreed. “In lupus, the treatment goal is always to lower steroid dosage to avoid toxicity without impairing the anti-inflammatory therapeutic effects,” he said. “Currently, we achieve this using some combination of hydroxychloroquine and immunosuppressants like cyclophosphamide. The *Nature* paper now suggests that the TLR7 and TLR9 dual antagonists could offer a third option for lowering steroid dosage.”

The findings “confirm the important role that TLR7 and TLR9 play in lupus pathogenesis and provide strong justification for antagonizing those receptors to block downstream production of IFN- α and other proinflammatory cytokines,” said Nicola La Monica, VP of biology at **Idera Pharmaceuticals Inc.**, which is developing a dual antagonist called IMO-3100.

Moreover, according to Coffman, by targeting TLR7 and TLR9 rather than IFN- α directly, “the antagonists block IFN- α signaling only in pathogenic immune cells, otherwise not affecting interferon levels that are important for the host antiviral response.”

Dual TLR7 and TLR9 antagonists have already shown efficacy in animal models of lupus and other autoimmune diseases.^{4,5} In addition, Idera’s IMO-3100 has shown safety and tolerability in a Phase I trial in healthy volunteers.

La Monica said Idera plans to decide on the phase and autoimmune indication of its next trial for IMO-3100 in the fourth quarter.

Dynavax’s lead dual TLR7 and TLR9 antagonist, DV1179, is in preclinical development for lupus and other autoimmune diseases. The company hopes to begin a Phase I trial in lupus within the next year, Coffman said.

Lars Rönnblom, professor of rheumatology at **Uppsala University**, thinks dual TLR7 and TLR9 antagonists could also be used in the disease outside the context of a steroid-sparing therapy. Because the antagonists “don’t primarily target downstream inflammatory events causing organ inflammation, but rather block a central autoimmune process that exists upstream, this approach may have the potential to induce long-term remission,” he said.

La Monica noted, however, that “monotherapy is generally not the way to proceed with the clinical development of lupus therapies. Consequently, in designing clinical studies beyond our initial Phase I safety trial, we will have to consider how best to combine our dual TLR7 and TLR9 antagonists with steroids and other standard of care for lupus and other autoimmune diseases.”

Ignacio Sanz, professor of medicine, microbiology and immunology at the **University of Rochester Medical Center**, had some suggestions for designing such a trial. “One could consider a study in which

lupus patients with moderately active disease and who receive moderate amounts of immunosuppressants would be treated with either a tapering dose of glucocorticoids plus TLR7 and TLR9 inhibitors or glucocorticoids plus placebo,” he said.

Last week the FDA issued final guidance on the development of products to treat systemic lupus erythematosus (SLE) and lupus nephritis. For SLE trials, the agency recommends primary endpoints of reduction in disease activity, complete clinical response or remission, reduction in flare or increase in time to flare, reduction in concomitant steroids and treatment of serious acute manifestations.⁶

The most advanced targeted lupus therapy is Benlysta belimumab, a human anti-BLyS (BAFF) mAb from **Human Genome Sciences Inc.** and **GlaxoSmithKline plc**.

In the Phase III BLISS-52 (Study of Belimumab in Subjects with SLE) and BLISS-76 trials to treat SLE, the 10 mg/kg dose of Benlysta plus standard of care met the primary endpoint of significantly improving patient response rate at week 52. The 1 mg/kg dose met the primary endpoint only in BLISS-52.

Last month, Human Genome submitted a BLA to the FDA and GSK submitted an MAA to the European Medicines Agency (EMA) for SLE.

Coffman told *SciBX* that a patent application has been filed on the *Nature* findings and that GSK has an option to obtain an exclusive license to that IP. In 2008, Dynavax and GSK partnered to discover, develop and commercialize TLR inhibitors to treat diseases including lupus, psoriasis and rheumatoid arthritis (RA).

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COMPANIES AND INSTITUTIONS MENTIONED

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GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Human Genome Sciences Inc. (NASDAQ:HGSJ), Rockville, Md.
Idera Pharmaceuticals Inc. (NASDAQ:IDRA), Cambridge, Mass.
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