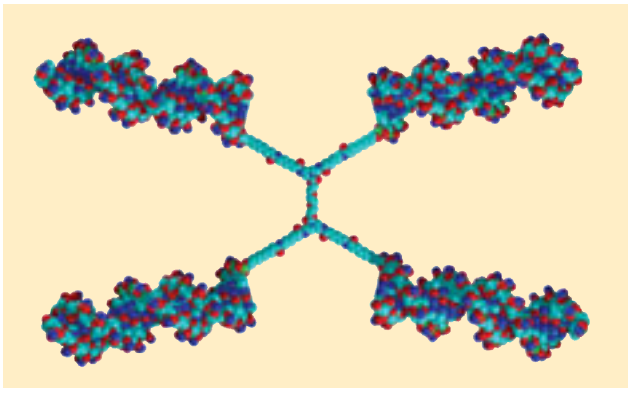
A new drug for lupus?

Like the disease it targets, the case for Riquent is not clear-cut.

BY DAVID FILMORE

Riquent, the next systemic lupus erythematosus (lupus, for short) treatment up for review by the FDA, has a lot of history to overcome.

There has not been a newly marketed drug for lupus, an autoimmune disease currently affecting more than a million people (predominantly women), in more than 30 years. The last lupus New Drug Application (NDA)—for Aslera, a synthetic formulation of the human hormone dehydroepiandrosterone (DHEA), by California-based biotech firm Genelabs Technologies—was met with a "not-approvable" letter from the agency in 2001. Subsequently, Genelabs changed the drug's name to Prestara and submitted additional data that improved its chances but required an extra Phase III trial now ongoing. At least two other companies have started early-stage clinical trials for lupus drugs in the past five years and stopped them because of problems with safety or efficacy.



Riquent, represented above, targets B cells that produce autoantibodies to double-stranded DNA by presenting these molecules to a patient's immune system. (Image courtesy of La Jolla Pharmaceutical Co.)

And the NDA for Riquent, submitted in February by another California firm, La Jolla Pharmaceutical, is by no means an open-and-shut case. "The overall argument is that the totality of the data seems to be going in the right direction and that lupus is a tough area to work in," says Steven Engle, La Jolla's CEO. "There is not really a clear and easy regulatory pathway," he laments.

Lupus can potentially damage just about every organ, from the skin and bones to the brain and kidneys, and it often does so very unpredictably.

"You never know what your cells are plotting against you," is how Jill Buyon, vice chairman of rheumatology at the New York University Medical Center's Hospital for Joint Diseases and lupus specialist, put it at a session on lupus at the Biotechnology Industry Organization's CEO & Investor conference in February. "The disease activity is intermittent, with or without therapy, making the determination of efficacy and safety sometimes difficult."

This makes designing definitive clinical trials a challenge.

One option is measuring changes in global disease indices, which apply different mathematical weights to various disease symptoms—ranging from seizures to arthritis to headache to elevated protein levels in urine. The most common of these is the systemic lupus erythematosus disease activity index (SLEDAI), which is an important component of Genelab's NDA.

Another, and possibly more straightforward, alternative is to focus on improving a particular organ system. La Jolla has taken this approach with Riquent, which targets lupus nephritis, or kidney involvement—the most common cause of morbidity and mortality in patients.

This strategy comes with its own difficulties, however, stemming from the powerful medicines—corticosteroids, such as prednisone, and immunosuppressants, such as cyclophosphamide—often used in high doses for treating lupus nephritis. These treatments can cause what Buyon describes as "incredible ravages," including osteoporosis, diabetes, infection, and permanent sterility. These toxic consequences are a primary reason that a new lupus drug is so urgently needed, Engle believes.

But at the same time, these medicines can be quite effective at quelling lupus disease activity. This can make proving efficacy for a new drug, in a trial in which both the experimental and control groups are taking steroids and immunosuppressants, very difficult. "Try as you may," Engle says, "you may not be able to [statistically] get rid of all of their effects."

He partly blames other drug effects for Phase III trial results announced in February 2003, in which improvements were observed for the primary end point of time to renal flare (kidney inflammation), but they were not statistically significant.

Nonetheless, Engle is optimistic that Riquent will be approved, possibly with the help of a truncated regulatory protocol that has been used to accelerate the path to market of some anti-HIV and cancer medications.

Unlike DHEA, Riquent goes after a specific target in a lupus patient's "self-attacking" immune system. Its target—antibodies to double-stranded DNA, or anti-dsDNA—is one of very few markers found to be specific to lupus (although it is not a requisite for having the disease) and is particularly associated with patients suffering from kidney damage.

The drug is based on La Jolla's Tolerance technology, in which a carrier platform serves as a vehicle for presenting epitopes, in this case several variations of dsDNA, recognized by antibody receptors on a targeted B cell, causing the immune cell to undergo apoptosis.

"No one really doubts that the drug lowers the antibodies," Engle says, as it appeared to do particularly well in a large subset of patients La Jolla identified in a Phase II/III trial completed in 1999.

Initial analysis of those trial results, like the subsequent Phase III results, did not

show statistical significance in increasing time to renal flare or the secondary end point of decreasing dependence on high-dose corticosteriods and cyclophosphamide therapy. Subsequently, however, 213 trial participants were stratified by the affinity of their dsDNA antibodies to Riquent in a surface plasmon resonance assay. In the 89% of patients found to have high affinity for the drug, statistically significant improvements were observed for both end points.

"Based on that, we went to the agency and predefined the intent-to-treat group in the Phase III trial to be patients who had high-affinity binding to the drug," Engle explains. "We are prepared to have this assay available on the market once they tell us that we can launch the drug."

However, reduction of anti-dsDNA in the intent-to-treat patients taking Riquent compared with placebo was the only Phase III trial end point that ended up reaching statistical significance.

But further analysis produced somewhat more promising results. For all Phase II/III and Phase III trial participants—placebo and Riquent groups—there was a statistically significant correlation between sustained reduction of anti-dsDNA and a reduced risk of renal flares. La Jolla also found a correlation between anti-dsDNA reduction and improvements in a standardized quality-of-life assessment. These findings present a "connect-the-dots" type of argument.

"It appears as though lowering antibodies is good for patients," Engle explains. "So if it lowers antibodies and lowering antibodies is good for patients and the drug seems fairly benign, then we probably ought to move ahead with the drug."

Under a particular section of FDA regulation, called subpart H, this line of reasoning could potentially hold water. Subpart H allows accelerated approval of a drug for serious, life-threatening diseases of unmet need on the basis of a surrogate end point considered "reasonably likely" to predict clinical benefit. Following approval, however, the drug has to be put through a Phase IV trial while it is on the market.

LA JOLLA PHARMACEUTICAL CO.

"There is not really a clear and easy regulatory pathway" for lupus, says Steven Engle, CEO of La Jolla Pharmaceutical Co.

"This next trial has to be done and has to show clinical efficacy, or that drug will be pulled," Buyon warned investors in February.

More than 40 drugs have been approved under subpart H since the early 1990s, including Norvir and Viracept for HIV and, more recently, Gleevec and Iressa for cancer.

La Jolla first plans to try for a full-fledged, nonaccelerated approval based on its Phase III results. Although lacking statistical sig-

nificance, there was a 30-month time to renal flare difference between the Riquent and placebo groups, and the trial showed a very good safety profile, Engle says.

But on the basis of previous discussions between La Jolla and the FDA, the review will be set up so that if this argument is deemed insufficient, the agency will move immediately to consider the feasibility of anti-dsDNA as a surrogate end point under the subpart H regulation.

Buyon, a voting member of the FDA Arthritis Drugs Advisory Committee, stated in February that anti-dsDNA had not yet reached the threshold to be a surrogate marker, "although we may be getting close," she commented.

The Arthritis Committee discussed lupus clinical trial end points with the agency at a September 2003 meeting, although it was not making recommendations on any specific drug application. (The Cardiovascular and Renal Drugs Advisory Committee, and not the Arthritis Committee, will review the Riquent data.) The Arthritis Committee expressed interest in using anti-dsDNA as part of a "composite" end point but had some concern that it may not be established enough to work on its own.

Engle asserts, however, that the committee's comments were "consistent with what we are attempting to do."

He also stresses that the great imperative for a new lupus treatment should play an important role in the subpart H deliberations. "There are patients who will tell you that they would rather have been diagnosed with cancer."

"How high a hurdle do you want in lupus? If not this drug, with this profile, when will you get a drug?" he asks. "Because everybody that goes into the area is going to face similar kinds of problems."

Whatever path it takes, the NDA decision, which Engle expects by October, could provide some clarity for future lupus drug development Engle now wishes he had. Meanwhile, Elusys Therapeutics, which urged the FDA at the September Arthritis Committee meeting to recognize dsDNA autoantibodies as a surrogate marker, has completed two Phase I trials for ETI-201, which uses the company's heteropolymer technology to target anti-dsDNA in lupus patients. And Human Genome Sciences is performing Phase II trials for its monoclonal antibody lupus candidate, LymphoStat-B, which targets a protein the company says is required for the development of mature plasma B cells.

"We are essentially validating outcome measures for the next guy," Engle says. He likens the situation to antitumor necrosis factor therapies for rheumatoid arthritis that first reached the market in the late 1990s. "Until these products came along," he says, "there was no way to determine how important the tumor necrosis factor was. There is an extremely interesting parallel in my mind that, in lupus, it takes a drug that lowers dsDNA antibodies to really help you understand how important they are." ■